SCIENCE

10 April 1959

Volume 129, Number 3354

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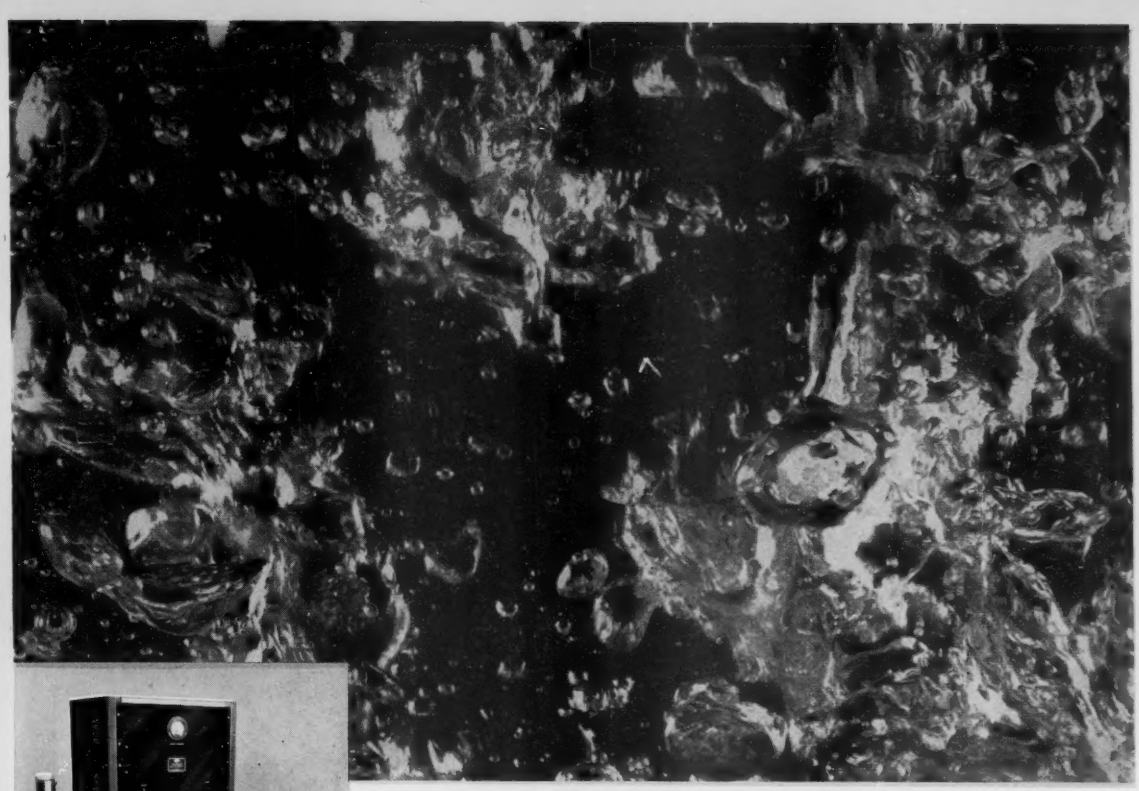

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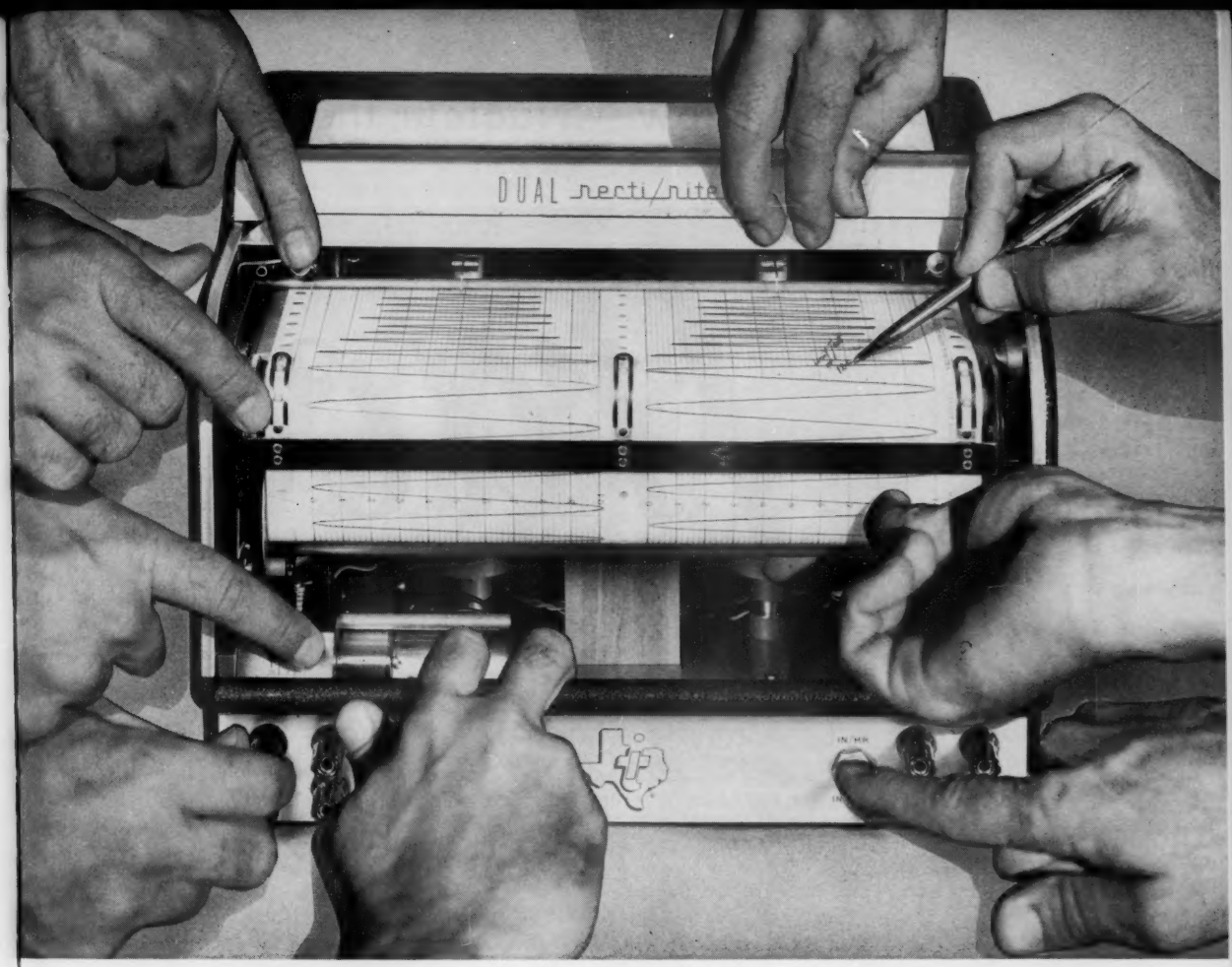

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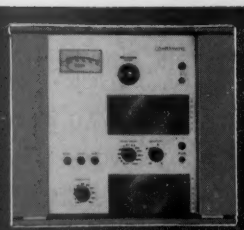

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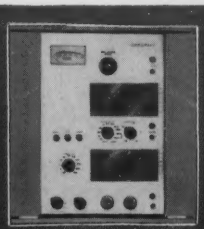

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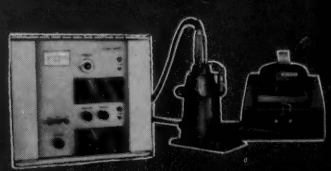

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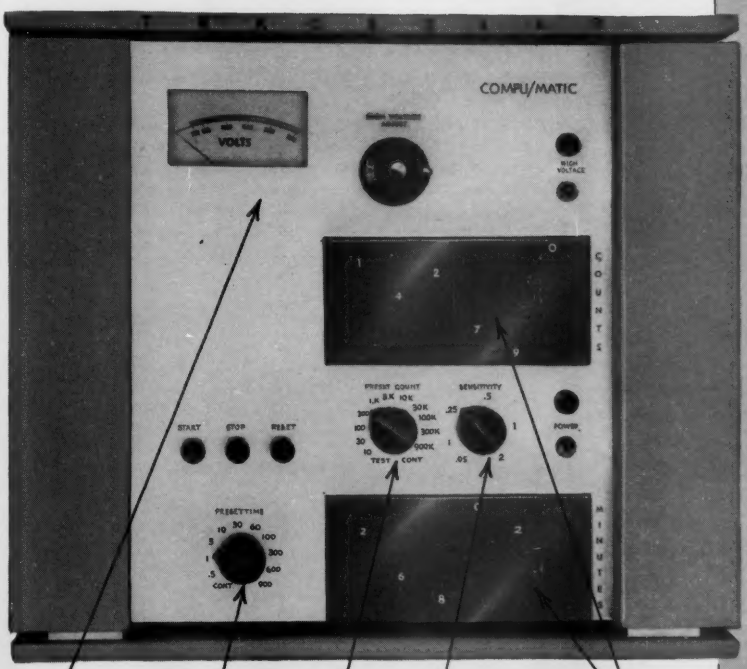


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AUTO-COMPUTER

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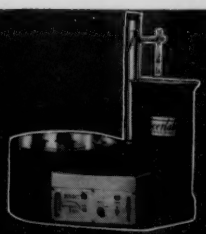

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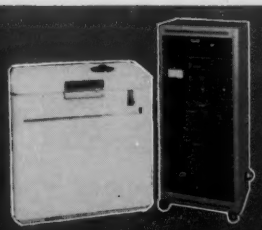

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William Whewell...on mind and matter

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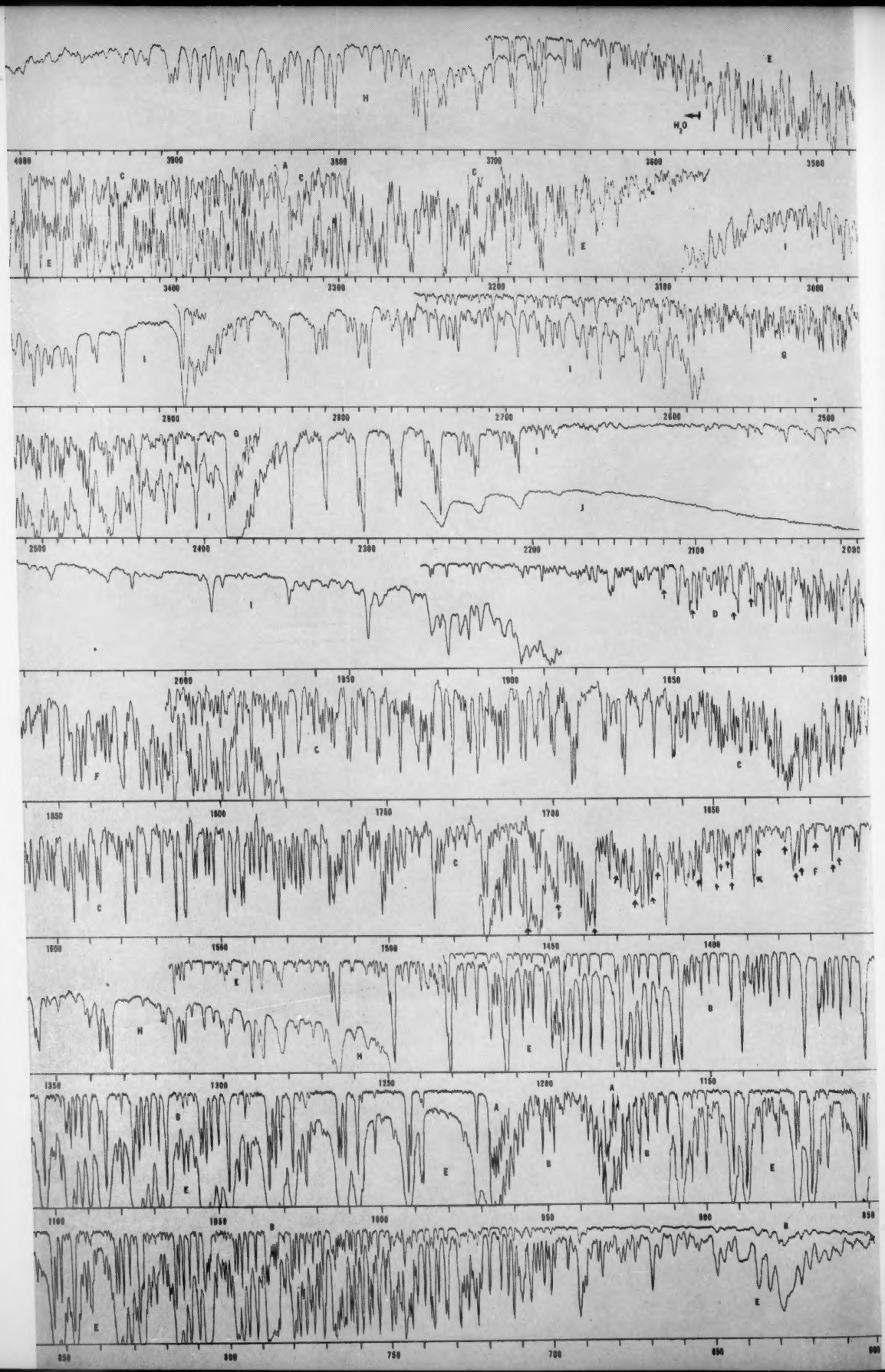
—*Philosophy of the Inductive Sciences, 1847*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Letters

Experimenter and Subject

The article by James G. Holland [*Science* **128**, 61 (1958)] on experiments on human vigilance arouses in me certain immediate and delayed reactions based on long experience as a chemical engineer dealing with observation of experimental phenomena. The author's observation that an empirical examination of the data per se must come first, without too early a development of theories, is most pertinent; such an approach is the basis of good experimental work. I do feel, however, concern over seeing data presented and not correlated (though perhaps the author has attempted correlations, with little success). Examples of such data are the length of the period following detection in which no observing responses are emitted as a function of the fixed-interval length; the slope of the response curve as a function of time of exposure to the type of interval, and so on. The data on the behavior of two different subjects, given in the same graph (in Fig. 7), together with the more elegant and meaningful treatment in Fig. 9 of a group of high-response versus a group of low-response subjects, certainly suggests the need for a reexamination of earlier work in terms of subject ability.

In raising these and other questions I realize that the immediate response will be that this is "outside one's field," an area in which one has "no competence," and so on. This brings to mind the general separateness of the specialties, deplored by some and rigidly maintained by most. A pertinent remark is that of a physicist who criticized a piece of chemical research and was told off for getting out of his field of competence. The physicist replied, "I may not be a chemist, but I know poor research when I see it." This is not to imply, I hasten to add, that the subject research, or all other research in that field, is poor research work, but rather that there is a common basis of examination characteristic of good research men confronted by data from any field. A virtue of *Science* is its presentation of fairly raw data with sufficient description of the experimental conditions to enable one to begin to assess the experiment as an experiment, without regard to the background literature. To paraphrase what Holland notes, one can criticize and correlate data without a theoretical basis pertinent to the literature and without development of theoretical concepts relating to other work.

To return to the experiment at hand, it would appear pertinent to consider the ability of the subject at the job in question and his demonstrated skill for the work. Thus, taste tests must utilize subjects with taste-discrimination, if sensitivity is required. Pertinent in this case is the response of subjects with radar search experience on live targets, as compared with subjects new to this type of operation.

A related question is the inherent or partially developed ability to correlate experiences, such as is found in a trained investigator studying an apparatus, who must develop suitable controls to make it operate properly. Similarly, a nonprofessional operator of a distillation tower or a furnace or other device will often develop an unusual ability to relate cause and effect in controlling the operation. Is this learning, or is it a demonstration of ability to think deductively about one's relation to the environment? How often did Newton observe the fall of an apple before wondering about it?—if we may believe the simple story of our childhood. In a sense, the described experiment is a contest between the experimenter and the subject, and perhaps it should be examined in that light.

JAMES H. WIEGAND
Sacramento, California

European Degrees

The article "Basic research in Europe" [*Science* **128**, 227 (1958)] by D. M. Gates, is most interesting—but I can't agree with his "translation" of European degrees [for example (page 228) *licentiat* as "poor Ph.D."]. It's true, it's most difficult to find the American equivalent for earned European degrees; I know it from personal experience. I hold the degree of "Dipl. Ing., Dr. techn."—that is, "Diplom-Ingenieur, Doktor der Technischen Wissenschaften," generally abbreviated "Dr. Ing." (set before one's name)—but no United States authority could give me a dependable answer to the question of how to "translate" these degrees. I'm using "D.Sc. (Tech.)"; others call themselves Ph.D.'s. The "Dipl. Ing." (in chemistry) is sometimes "translated" as Ch.E. or M. Eng.

I believe it would be desirable for some authority—federal or organizational—to standardize the "translation" of foreign degrees, and for the holders of honorary degrees to indicate them by setting an "h.c." (*honoris causa*) after the "Dr." or "D.Sc.," as is customary in (Central) Europe.

Couldn't the AAAS, together with the American Institute of Chemists, the American Chemical Society, and others, initiate steps to end the confusion?

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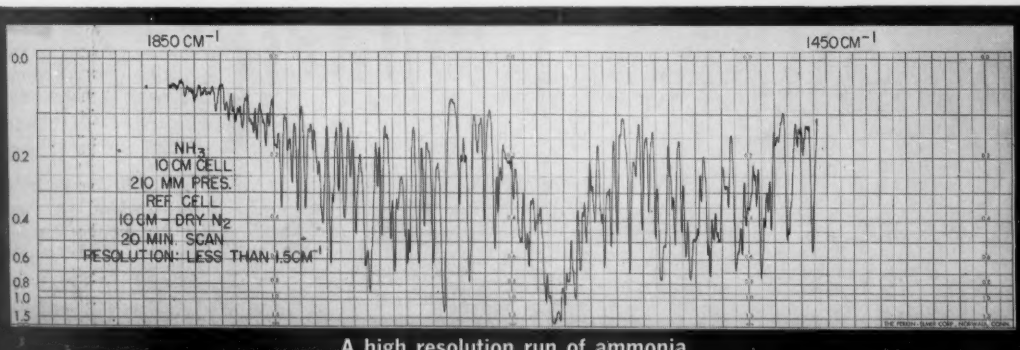

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SCIENCE

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The value of good library collections and facilities is recognized by all scholars and professional scientists. So far as the general public is concerned, a greatly increased awareness of the role of the school library in education is needed. High-school libraries are a fairly common adjunct of the public educational system, but many of them are not good, and all too often they are in the charge of an over-worked teacher instead of a trained librarian. A still smaller percentage have adequate collections of up-to-date science and mathematics books. A survey of the library holdings of approximately 1000 representative American high schools conducted by the AAAS during 1958 disclosed that only 5.1 percent of the books were devoted to science and mathematics. Considering the portion of the school curriculum devoted to science and mathematics, not less than 20 percent of a high-school library's holdings should be in this area.

The importance of good library facilities is recognized in Title III of the National Defense Education Act of 1958 (Public Law 85-864, 85th Congress; 72 Stat. 1590) which makes funds available for "acquisition of . . . printed materials (other than textbooks) for use in providing education in science, mathematics, or modern foreign language, in public elementary or secondary schools, or both, . . . " Standards for the improvement of instruction in science, mathematics, and modern foreign languages formulated by the Council of Chief State School Officers emphasize "that the provision of better materials and equipment would result in more efficient learning and better adaptations of the educational programs to individual differences, both for the academically gifted and for those whose talents lie in other fields."

The AAAS Traveling Science Library Program, supported by an annual grant from the National Science Foundation, is immediately concerned with the improvement of school libraries and the enlargement of their role in science education. The Traveling High School Science Library, received currently by 1309 senior high and private preparatory schools, is enriching science and mathematics courses and accelerated and honors programs for gifted students.

Plans are now being developed to initiate a Traveling Elementary Science Library Program in the fall of 1959 which will be made available to 1000 selected elementary and preparatory schools, particularly those that are giving special consideration to the gifted student. Science Service, in administering the Westinghouse Science Talent Search and the National Science Fairs, has determined that the majority of the winners developed their science interests before they entered junior high school.

The celebration of National Library Week is indeed appropriate, but achievement of lasting results in education will come about when every week is National Library Week.—HILARY DEASON, *AAAS*

10 April 1959, Volume 129, Number 3354 SCIENCE

Antigens and Antibodies as Cell Phenotypes

How does cell heredity change when host-graft relations are altered or antibody formation is stimulated?

Jack Schultz

The brilliant experimental successes of recent years, which have shown a basis for the behavior of tissues on transplantation in immunological and genetic phenomena, seem now to be ranged in two sharply contrasted bodies of data. On the one side, the rigorous "laws of transplantation" demand a community of genetic constitution between host and implant for the graft to take (*1*); the antigenic constitution of the tissue in this regard is as directly related to the specific genotype as are the classic immunological blood groups. Contrasted with this definite picture are the experiments in which tolerance is induced, or histocompatibility barriers are overriden, or tumors are enhanced in their growth or adapted to their hosts. Similarly, when the cellular basis of antibody synthesis is considered, analogous problems in cell heredity appear. It is the object of this article (*2*) to consider how far the genetic analysis in quite another field—that of the serotypes of ciliate Protozoa—may be helpful in unifying these contrasts and also to explore what known mechanisms operating in the chromosomes may be common to both systems.

Change in Transplantation Specificity

A genetic analysis of differences in histocompatibility factors (*3*), as Snell has called them, is made by determining the frequencies with which tissues from inbred strains of mice will become established as grafts in the progenies of hybrids between them. In the F_1 hybrid, both parental types of graft will take. In the backcross, or in the F_2 generation, the frequency of take is a measure of the different genetic types segregating out according to Mendelian expectations. Thus, in the mouse, largely as the result of the work of Snell and his colleagues at Bar Harbor, at least 15 loci are believed to be concerned with these differences. Three have been more closely analyzed than the others, and in the case of the so-called H-2 locus, have now been dissected into a system of pseudoalleles, also responsible for blood antigens. The conventional precision of the genetic picture is remarkable.

This situation, straightforward in principle even though complex in its details, becomes involved when experiments of another kind are considered. The initial discovery of the phenomenon we owe to Barrett and Deringer (*4*). They found that tumors, after a passage through F_1 hybrids between their strain of origin and some other, will undergo a change in the frequency of take when tested in the F_2 progenies or in backcrosses of the two strains. Moreover, a specific relation to the nature of the F_1 hybrid in which the change occurred was suggested: the increase in compatible grafts occurred only with F_2 or backcross progenies involving the same two strains.

Hauschka (*5*) extended this description in two ways: he found cases of change, after F_1 passage, in which the specificity of the graft was increased rather than decreased, and—more important—he interpreted the numerical data as showing a change in the number of histocompatibility gene differences between tumor and foreign strain. With the discovery of a correlation between heteroploidy of tumor chromosomes and an increase in host range on transplantation, it became apparent that selection of favored antigenic types among the population of cells in the implant could occur, and that it would be dependent on the constitution of the host (*6*). This interpretation of "immunoselection" was extended easily to the Barrett-Deringer phenomenon, in place of their original term, "adaptation." But this extension seems now to have been incorrect.

The recent important studies of Eva and George Klein (*7*) go far towards excluding the selection interpretation. The Kleins established a number of sublines, derived from small inocula of a single tumor, and made comparisons of frequency of take in F_2 populations between these and lines derived from the same tumor after passage through F_1 hybrids. In this material a direct test could be made of the hypothesis that cells of the type predominant after F_1 passage were already present in the original population and were merely selected out by the F_1 hybrid passage. Mixtures of the two types of cells (one "adapted," 70 "original") tested in the segregating F_2 population showed frequencies characteristic of the "adapted" type; hence, if these cells had been present even in relatively low numbers in the original tumor, no effect of the F_1 hybrid passage could have been detected.

Moreover, by short-term experiments in an Algire diffusion chamber (*8*), the Kleins were able to show that the effect occurred before displacement of one type by the other on a selective basis could operate. Since it is supposed that no cells pass through the walls of the diffusion chamber, these experiments also

The author is chairman of the division of biology of the Institute for Cancer Research, Philadelphia, Pa.

indicate that the change does not require cell-to-cell contact but may be mediated by humoral factors, in contrast to the homograft reaction itself (*8*). The Kleins, following a suggestion by Medawar regarding tolerance (*9*), incline towards the view that the F_1 hybrid effect may be a change in the reaction of the tumor to the antibodies it provokes in the host; they mention experiments with preimmunized animals as evidence that the change involves, not a difference in the antigenic composition, but rather an increased resistance to isoantibodies.

Serotypes in Paramecium as a Possible Model System

These two groups of experiments—the one showing orthodox genetic regularity, the other indicating a genetic lability—provide a model of a now recurrent problem in transplantation experiments. They present a dilemma—that of distinguishing between genotype and phenotype—which is not new to genetics (*10*). As a guide for such an effort, the analysis of possibly parallel cases in the ciliate Protozoa, especially *Paramecium,* by Sonneborn, Beale, Preer, and their associates (*11*) may be examined. These systems present obvious analogies, which have been recognized and mentioned on several previous occasions (*12, 13*).

In *Paramecium,* the criterion of antigenic constitution originally used by Sonneborn is the immobilization of the cell when exposed to its specific antiserum. Each clone therefore has its own serotype. Latterly, using fluorescein-labeled antibodies, Beale and Kacser (*14*) have shown that the antigen-antibody reaction takes place at the surface of the cell.

The study of different strains disclosed a diversity of antigenic constitution, and with the rich experimental techniques available in *Paramecium,* it was shown that the inheritance of the serotypes could be cytoplasmic in certain crosses but in others followed a strict Mendelian pattern. The apparent contradiction was beautifully resolved by proof that the same genotype could be compatible with the expression of a variety of different, in most cases mutually exclusive, cytoplasmic states. Take, for example, a clone of *Paramecium* exposed to its own antiserum; the immobilized individuals recover and are allowed to grow. Now, when the paramecia are tested, although the reproduction has been purely vegetative and the genotype is constant, the antigenic constitution has changed and is stabilized in a new form. These serotype transformations occur as a response to a wide variety of environmental stresses; the weight of opinion now tends towards the conclusion that any factor upsetting the general metabolism of the cell may begin the process and that its course in a given serotype during the ensuing cell divisions (during the process of differentiation, so to speak) depends on the environmental conditions (nutrition, temperature, and so on) for cell metabolism. When all these conditions are specified and remain constant, proper analysis of crosses shows a number of loci each represented by a range of alleles, each allele being responsible for a special serotype. Moreover, studies of heterozygotes afford evidence for the independent action of each allele present.

In a *Paramecium* of a specified genetic constitution, therefore, the serotype manifested represents the activity of one of a group of loci capable of affecting its antigenic constitution. Which locus is expressed in the cytoplasmic state depends on the constellation of factors at the time the pattern of antigen synthesis is set. The possible nature of the response in the nucleus is discussed in a subsequent section; yet it should be noted here that the analysis of phase change in the *Salmonella* antigens (*15*) has shown, by transductive techniques, that these antigenic changes are governed by a nuclear event in a system which also involves the mutual exclusion of antigens.

Change in Tumor Host Specificity

This analysis provides a model of cell heredity maintained through the cytoplasm, yet withal based on orthodox Mendelian principles. The possibility of an analogy between these cases and those encountered in the immunogenetic systems of mammals has not been entirely disregarded in previous discussions. However, if one takes the Barrett-Deringer phenomenon as a point of departure, a more explicit analogy may be drawn, which has consequences for future experimental design.

The homograft reaction, like the serological test, gives a first-order analysis of the specific antigens present in a cell type. In contrast to the situation described in the *Paramecium* serotypes, however, each of the antigens responsible for the homograft reaction appears to manifest itself independently of the others; the similarity to such immunogenetic cases as the blood groups is obvious. The different loci concerned are not all equivalent in their influence: the H-2 locus (the most studied), at which some half-dozen separate antigens have been shown from the different alleles (*3*), is the determinant in any situation where differences exist for it between graft and host. The other, weaker loci require special conditions of cell dosage, preimmunization of the host, and so on for unequivocal demonstration, as Snell (*16*) has found.

In the present context, it is important that these are the factors presumably affected by the F_1 passage; for the Kleins (*17*) have found no evidence of an F_1 effect in strains of tumors differing at the H-2 locus. It therefore follows that the weaker systems are those with which we are presently concerned, and the indication that preimmunization may obliterate the distinction between an F_1-treated tumor and its original type signifies that the effect of the passage is somehow on the quantitative relations of the immunological response. Thus it is conceivable that the effect of the passage on a specific locus is to change its activity.

In the *Paramecium* serotypes, transformation consists in the replacement of the products of the activity of one locus by those of another. It therefore consists of two phases: the triggering of activity at a locus and the displacement of the accumulated product of the old locus. The mosaic character of the histocompatibility antigens limits the analogy with the *Paramecium* system: the possible occurrence of competing steady states, so important in the discussions of the cytoplasmic states in *Paramecium,* does not concern us here. The question is the mechanism whereby change in the effective amount of a single antigen may occur. In terms of the *Paramecium* analogy, this is the initial triggering reaction, which occurs in the parental-strain tumor cell that is implanted in the F_1 hybrid.

Since the Barrett-Deringer effect shows a high degree of strain specificity, the influential factors in inducing the change are most reasonably sought in some immunological reaction, involving either the antigens themselves or some substances complementary to them. These must be supposed to enter the cell and, by cross-reacting with the antigen-producing system at the critical locus, to set up a new condition of cell heredity with respect to the histocompatibility effects at that locus. Formally, this is comparable to a directed somatic mutation, and the value of the *Paramecium* anal-

ogy lies precisely in the fact that it dissolves the formal terminology and necessitates more concrete thinking.

One line of speculation is the following: The loci manifesting the Barrett-Deringer effect are, as has been said, all "weak" loci—a condition interpretable as resulting from a tendency not to release antigen (or to form just enough to maintain what is needed for the cell economy). Hence, the formation of antibodies, whether circulating or cell-bound, lags in these types, and the histocompatibility barrier is easily vaulted. The exposure of cells containing such loci to the foreign antigens of the F_1 hybrid allows competitive conditions to be set up, in which the cytoplasmic state for the particular locus is changed. Either by the formation of antigens of a different type or by a change in the rate of antigen formation, the ability to elicit the homograft reaction is reduced, and this leads to an apparent decrease in the number of histocompatibility differences manifested in the test cross; or the ability to elicit the homograft reaction may be increased at a locus where the response was subliminal in the original line, before the F_1 passage, and this leads to an apparent increase in the number of factors required.

An alternative line of speculation emphasizes a possible increase in the resistance of the cells to the antibodies they elicit. This point of view, already envisaged by Klein in terms of "tolerance," suggests as a mechanism the kind of zone effect considered as a possibility for explaining the nonspecificity of heteroploid tumors (*18*) and elaborated for certain cases by Feldman and Sachs. Here the quantitative relations between antigen and homograft antibody are believed to be so changed that the amount of antigen in the cell as compared with the antibody available in its environment exceeds or fails to reach a critical ratio for occurrence of the homograft reaction.

Whichever of these possibilities is shown to be the actual mechanism (experimental tests suggest themselves, in which Snell's isogenic resistant lines are utilized), the essential mechanism of the adaptation in either case could be the activation of a new cytoplasmic state, in terms of the *Paramecium* analogy, but differing from *Paramecium* in that each locus conditions a state relatively autonomous of the factors at other loci. In both cases, the mechanism consists in the response of the cell to an environmental stress by the establishment of a new pattern of synthesis, stable under the new conditions.

Actively Acquired Tolerance and Enhancement

Now it is appropriate to consider whether the analogy with the ciliate serotypes can hold for other types of change in transplantation specificity. Those that come immediately to mind are the tolerances induced either in tumors, by implantation into organisms whose immunological system is not yet functional, or in immature organisms, by the implantation of foreign tissues. These are recognized as changes in the heredity of the cells in which they occur. Together with them we may consider the phenomenon investigated by Kaliss (*19*)—the enhancement of tumor growth after implantation in foreign-strain animals previously inoculated with frozen-dried preparations from the tumor. This also may be an effect not on the immunological system of the host but on the nature of the tumor cell itself. An interesting relationship exists between the time of inoculation and the time of implantation; only after the immune response tails off does the enhancement appear. This phenomenon, like certain other adaptations, seems not to be permanent but to be reversible after a number of transfers and to involve the H-2 locus.

Many of these phenomena may be susceptible of explanation in terms of "immunoselection," as Hauschka has used the concept—to account for the displacement of specific diploid by nonspecific heteroploid tumor stem lines. Yet the existence of one case in which the selection hypothesis has been disproved makes it advisable to consider in these others, also, whether the concept of the genetically controlled cytoplasmic state may not be useful.

The enhancement phenomenon, with its relation to the immunological system of the host, offers in some ways a more direct parallel to the *Paramecium* cases than does the F_1 hybrid change. For here there are present antibodies to the tumor which, by their reaction with the tumor antigens under conditions in which the tumor cell is not destroyed, trigger the establishment of a new compatible cytoplasmic state for the loci of histocompatibility difference. It should be noted that Kaliss has not yet found any permanence of what he believes to be the enhancement change; this difference from the Barrett-Deringer phenomenon may be a characteristic of the H-2 factors involved, or it may indicate a real difference in mechanism (such as antibodies involved for enhancement versus antigens in the F_1 hybrid).

As already mentioned, Klein has considered the possible relationship of the Barrett-Deringer phenomenon to the induction of tolerance towards foreign-strain tissues in animals implanted with the foreign lymphoid or bone-marrow cells while in the fetal state, or when new-born (*20*). The original case in cattle (*21*) contains the essentials: Twins different in their genetic constitution, but having had a common placental circulation, turn out to be mosaics (or chimeras) with respect to their blood cells. Each of the twins has cells of two blood types, representative of their respective genetic constitutions; thus, each genotype is now tolerated in the foreign host. When skin transplants between such twins are made, instead of being rejected, they are maintained. In a series of admirable investigations (*20*), the phenomenon has been explored in detail in rodents and in fowl, with the conclusion that a change in the central immunological apparatus has occurred. Some of these experiments—for example, those with the cattle twins—are in essence mutual transplantations of tissues between embryos, in which immunological tolerance develops as the tissues differentiate. Where the adult lymphoid tissues are injected into the fetal or neonatal animal, apparently the tolerance reaction occurs only in the differentiating embryo, since the implant itself will eventually form antibodies against its host.

Initially, the association of the tolerance-inducing antigens with a nuclear fraction from the cells encouraged the speculation that these were involved with the deoxyribonucleic acid (*22*) and that some kind of transductive process might be occurring (*23*). More recent evidence tends to minimize this possibility (*23*). Obviously, proof of a transductive process necessitates genetic markers, and where these markers are present in the blood antigens of cattle twins, Owen (*24*) has emphasized that only the two types of blood group expected from the nature of the cross occur. In this case at least there is no evidence of the free and frequent transduction that would be required for tolerance.

The application of the *Paramecium* serotype transformation analogy to the induction of tolerance follows much the same line as application of the analogy in the F_1 change. Here the environmental shock comes from the foreign antigens of the implant, which would be presumed to change the cytoplasmic state of the differentiating cell from a condition reactive to the foreign antigen to one in

which the mature cell no longer responds by the synthesis of antibodies. The criterion of the change is complementary to that observed in the tumor cell. The change in the tumor cell in the F_1 hybrid is in the relation of its antigens to the hosts' antibodies; the change in the tolerant host is in the cells of its immunological apparatus, which no longer respond to the specific foreign antigens of the kind injected while these cells were maturing.

The apparent critical nature of the stage of differentiation for the induction of tolerance suggests that the realization of the histocompatibility factors may be one of the terminal stages in the differentiation of tissues and places this problem in the general field of embryonic differentiation. Mitchison (*25*) has provided evidence of cell multiplication for antibody-producing cells in the transplants of immunized lymph nodes; it follows, therefore, that the difference between mature and immature cells in these tissues is not simply a matter of the possibility of multiplication. Whether mature lymphoid cells, subjected to foreign substances (antigens or antibodies) under conditions in which they may multiply before the host's defenses come into action, can respond by the establishment of a neutral state (now tolerant of the host antigens) is a matter of conjecture. This is indeed what the tumor cells seem to be doing, both in the F_1 change and in the experiments reported by Koprowski (*26*) in which tumors were injected into fetal, foreign-strain mice. A variety of response from tissue to tissue is perhaps to be expected here.

In summarizing the foregoing sketch, it seems fair to state that neither the phenomena of tumor adaptation nor those of actively acquired tolerance are inconsistent with a scheme derived from the *Paramecium* analysis: constant genetic constitution, responding to triggering environmental stimuli by cytoplasmic states of synthesis, special for each locus. In the *Paramecium* case, the states are in general mutually exclusive; the histocompatibility loci appear to act independently of each other, although the degree to which this is established may perhaps be questioned. In both the instances considered, the process of antibody formation is involved, and in fact the finest discriminations are provided by preimmunization of the hosts, as Amos *et al.* (*27*), the Kleins (*7*), and Snell (*16*) have indicated. Let us now examine the applicability of the serotype transformation analogy to antibody formation.

Antibody Formation

It is not necessary here to review the characteristics of the antibody response; the reader is referred to several recent symposia (*28*), and to the treatment in Burnet's monograph (*29*), for a guide to the relevant literature. The earlier theoretical treatments were dominated by an attempt to understand the chemical mechanisms whereby specific configurations within large molecules could be replicated; the various forms of template hypothesis were the fruit of these endeavors. With the refinement of histochemical techniques and the elaboration of the methodology of cell transfer, the cellular basis of the antibody response is now being emphasized (*30*). The complex of cells in the lymph nodes and in related tissues like the spleen emerges as the protagonist in the response to an antigen. The various accounts agree in distinguishing sharply between the cellular response to an initial exposure to antigen (primary response) and a later exposure (secondary response). By the use of labeled antigens, ample evidence of antigen entry into the nucleus of cells during the primary response has been obtained, but only a few cells are thus affected, and the number of these showing antibody is low. All these cells belong to a special type: the immature plasma cell. The appearance of antibody in the serum follows the differentiation of the plasma cells in the lymph nodes. The dramatic events follow the secondary injection of antigen: Now there are large numbers of plasma cells, in clusters and showing antibody; following this, the elevated serum antibody level characteristic of the secondary response makes its appearance. It thus appears that the first exposure to antigen establishes a mode of differentiation, while the second affords a relatively specific stimulus to proliferation.

It should be recognized here that the older template theories, according to which antibody formation depended on the folding of pre-existing globulin on a pattern provided by the antigen, are now obsolete. New protein is synthesized in the newly proliferated cells, and the more recent theoretical treatments have all recognized that there must be an increase in number of templates as the result of cell proliferation to account for the rich variety of experimental fact. Schweet and Owen (*13*), for example, call for a change in the nuclear heredity (not necessarily genic?) of the antibody-forming cell (deoxyribonucleic acid change), while Burnet (*29*) favors a specifically induced change of a cytoplasmic template system, which he calls a genocopy, associates with the ribonucleic acid containing granules of the cytoplasm and nucleolus, and believes to be capable of replication. Both these treatments avoid the requirement of the earlier theories for the continued presence of antigen in the cell to account for antibody formation after long periods of time. The possibility of antigen persistence is perhaps still not excluded, but this has always strained the bounds of credibility as a general proposition—all the more so with the demonstration that cell proliferation is part of the response to the antigen.

The parallel between Burnet's treatment and the *Paramecium* serotype analysis is evident, once attention is directed to it. But the application demanded is somewhat more complex than that envisaged either by Burnet or by Schweet and Owen. In both of these treatments the secondary response presents a problem, explicitly recognized as unsolved by Burnet. Schweet and Owen have the antigen acting at two sites, first in the formation of a new deoxyribonucleic acid template and subsequently as an inducer, acting to influence synthesis of templates (ribonucleic acid containing) for antibody formation. The influence on the secondary response is deemed to follow from the inducer action. In neither of these is there any inherent reason for the wave of mitosis in the specifically antibody-forming cells.

According to the serotype analogy it would be expected that the antigen would determine the formation of a cytoplasmic state, the nature of which is discussed below, capable of forming its complementary antibody. The problem appears in its clearest form in consideration of the secondary response: Why should the antigen-stimulated cells divide? Is there any basis for assuming that an antigen-antibody type of mechanism can be a stimulus to mitosis?

During the primary response, the mitotic activity is moderate; there seems in fact to be no evidence necessitating any specific high mitotic activity. The cytoplasm of such cells would, on this assumption, contain antibody (and it does, on the evidence of fluorescent antigens). The stem cells of this line are those that multiply in the secondary response. They are stimulated to do so by the presence of antigen. If, as is probable, they contain antibody, they afford the opportunity for the combination of antigen and antibody at the cell surface.

Here it is necessary to recall the distinction between a stimulus to growth by

increase in nuclear and cytoplasmic substance and by the partition of nuclear and cytoplasmic units into separate cells at mitosis. The varied nature of the antigens makes it difficult to conceive that they act to supply the materials for cell growth; it seems unlikely that the stimulus to mitosis is the result of an immediate growth process. The alternative view seems preferable—that the antigen itself acts as an inciter of cell division in the cells capable of forming or already containing the complementary antibody.

This suggestion, while new for the antibody system, has been the basis of attempts to analyze the nature of the stimulus to mitosis in the egg cell at fertilization. For some time, Tyler (*31*), in particular, has investigated the implications of the hypothesis that the egg contains substances complementary to those at the sperm surface, which take part in the fertilization reactions. Quite recently, Perlman (*32*) has shown the presence in the egg of antigens, the antibodies to which are capable of activating the egg—that is, of initiating mitosis in the way postulated for the reaction of antigen with antibody at the surface of the lymphocyte.

It must be supposed here that the stem cells of the plasmacytic line, which contain antibody as a result of the primary response, need only the stimulus afforded by a surface reaction to go into mitosis; and that this stimulus is provided by the membrane change resulting from antigen-antibody combination. The process is the converse of that described for the sea-urchin egg by Perlmann; in that case the antigen is in the cell surface, the antibody coming to it from the environment. But in both cases an antigen-antibody combination occurs at the cell surface to supply a stimulus to mitosis.

The consequences for the intensive nature of the secondary response are apparent. In a lymph node the cells already forming antibody would be stimulated selectively to proliferate, by the newly arriving antigen. Since the specific antibody-forming cytoplasmic state has already been established, the cells so stimulated would increase the response exponentially. Whether, coincident with the specific excitation by antigen, other neighboring cells are also stimulated to a degree is, obviously, a secondary question in this context; the focal point of the problem is, as has been stated, why the specific secondary response should occur.

Further possible parallels exist between the mitotic processes in the egg and those of the plasma cell: Tyler (*31*) has reported the blocking of cleavage by what appear to be massive doses of antibodies to a fertilizing preparation from the jelly layer of the egg. The phenomena of immunological paralysis by massive antigen concentrations [cited in (*21*)] (blockage of proliferation by an extensive antigen-antibody combination at the cell surface) stand in much the same converse relation to this as the selective proliferation of antibody-containing cells does to the activation of the egg.

After the foregoing presentation had been written, J. Lederberg kindly called my attention to the review of Talmage (*33*) and to the note of Burnet (*33*), in which a hypothesis of selective proliferation of antigen-modified cells is developed. Both of these treatments take as the point of departure the combination of antigen with a pre-existing antibody, along the lines of Jerne's natural-selection hypothesis. They differ from the foregoing presentation with respect to the role of the antigen in the primary response; here this response is considered to be in the nature of a change in cell heredity, the latter proliferative response being selective. The treatment presented in this article avoids the awkward assumption that the immunological cell system contains cells synthesizing all possible antibody structures; that of Burnet and Talmage, on the other hand, requires only one function of antigen—namely, its combination with antibody. Experiments on antibody formation in single cells along the lines of those carried out by Nossal and Lederberg (*34*) may serve as a means of distinguishing between these possibilities. With either view, the analogy with the initiation of mitosis in the fertilization process is helpful.

A word may be added anent the problem of self-recognition, so prominent in Burnet's thinking. From the genetic point of view, the loci concerned with self-recognition belong to the histocompatibility group. From the discussion of tolerance already presented, it is evident that the cytoplasmic states conditioned in the cells of the organism's defense systems would be neutral—that is, would form gamma globulins noncomplementary to the antigens present in their embryonic environment. These considerations, however, lead into the field also of growth regulation, discussed in terms of complementary substances by Paul Weiss (*35*) especially, and would take the discussion too far from its base to be dealt with here in detail.

A Possible Chromosomal Basis

In the foregoing discussion the attempt has been made to encompass three quite diverse types of cellular change in mammals in terms of a mechanism for cellular heredity worked out in ciliate Protozoa. Each of these phenomena has at one time or another been thought of in terms of the mechanisms of protein synthesis and their direction by template systems, and in recent times the templates have been identified with the deoxyribonucleic acid molecules found in the chromosomes. Particularly is this true for the antibody-synthesizing systems (*13*), and the suggestion has also been made for the tolerance system (*23*). But an explicit discussion in terms of known mechanisms operating at the chromosomal level, and effective for action on the cytoplasm, has been lacking, and I shall now venture to present one.

The dilemma presents itself clearly in the *Paramecium* case (*11*). The cytoplasmic state, though quasi-autonomous, is nevertheless under nuclear control. Once the pattern is set, the competitive inhibitions postulated for the different postulated cytoplasmic states could possibly account for the autonomy, but the setting of the pattern depends on a specific chromosomal locus. In nucleocytoplasmic terms, the same requirements appear in the other cases also: (i) a definite chromosomal locus must respond to the special stimulus; (ii) the response occurs independently in each chromosome, under most conditions thus far studied; (iii) a variety of alleles is possible at each locus, the loci being genetically complex.

During the past few years, a series of observations on the giant chromosomes of the Diptera have accumulated, which now provide a cytochemical model of chromosome behavior suitable for the activities under discussion. Both in the chironomids (midges), which have been studied in Bauer's laboratory, particularly by Beerman and by Mechelke (*36*), and in the Brazilian gnat *Rhynchosciara* (*37*), structural changes in the chromosomes ("puffs") occur at times and places appointed by the activities of the cells in which they reside. There is here a specific functional response of the genetic system, of the type posited by the immunogenetic reactions under discussion. The "puffs" are formed or regress according to the cell type and according to the cell's stage of development or of function. It may reasonably be supposed that such behavior is not limited to the giant chromosomes—

rather, that they are the extreme case of a general mode of action.

The cytochemical analysis of these puffs is relevant to the discussions of possible changes in the deoxyribonucleic acid of the nucleus. Schweet and Owen had to postulate that a change in the kind of deoxyribonucleic acid is a special property of the antibody-forming system in response to the antigen. But Breuer and Pavan observed a massive increase in Feulgen stainability of the bands concerned with puff formation, which they interpreted as an actual increase of deoxyribonucleic acid in this process. The suggestion was immediately made that here was evidence for the direct quantitative involvement of deoxyribonucleic acid in gene activity, different from its previously postulated function as a constant framework for secondary ribonucleic acid template formation. Proof of the local disproportionate increase in deoxyribonucleic acid has been provided by the work of Rudkin and Corlette (*38*) in my laboratory, in which quantitative measurements of ultraviolet absorption and specific extraction procedures on *Rhynchosciara* chromosomes were used. Similar evidence has been provided for a chironomid, with measurements of Feulgen stainability (*39*). These measurements, together with the tritiated thymidine incorporation studies of Ficq and Pavan (*40*), support the serious consideration of differential deoxyribonucleic acid synthesis as a regular mode of nuclear response. The degree to which this synthesis provides a mechanism for irreversible differentiation has not yet been adequately explored; it is sufficient to recall the fact that the occurrence of irreversible changes in nuclei during embryonic differentiation has been demonstrated by King and Briggs in the frog (*41*), and this must be taken into account in considering the genetics of somatic cells (*42*).

With the synthesis of a special deoxyribonucleic acid in response to a cellular stimulus, the possibility of the direction of the synthesis to a new kind of deoxyribonucleic acid no longer is completely *ad hoc*; the extra deoxyribonucleic acid of the puff permits speculations about changes in composition according to the supply of precursors and by a displacement of its normal protein from the deoxyribonucleic acid, which makes possible a new sequence of bases in the deoxyribonucleic acid chain. However this may be, it is to the ribonucleic acid system that we must look for cytoplasmic states; and here the electron microscope studies are useful. For the dense ribonucleic acid containing granules, which with a complex of double membranes form the endoplasmic reticulum of cells [the framework of the cytoplasm (*43*)], are found in the nucleus also, and Gay (*44*) has shown a relationship in the salivary-gland nuclei of *Drosophila* between structures derived from particular loci on the chromosome and the endoplasmic reticulum of the cytoplasm. In mammalian cells, it appears that the nuclear membrane is part of the endoplasmic reticulum (*45*), affording thus perhaps a direct line of communication between the nucleus and the exterior of the cell. The point of this exquisite detail is obvious: it provides the possibility for reactions of specific loci on the chromosome to special groups of environmental changes. There is no need to elaborate such possibilities; they provide a basis for the specific reactivities that have been discussed, whose experimental analysis is still in its infancy. The integration of this structural analysis with the concepts of enzyme induction (*46*), from the permeases at the cell surface to the synthesis of the specific deoxyribonucleic acid in the nucleus, is a challenging problem.

This discussion, by one more familiar with chromosomes than with immunological reactions, only serves a purpose if it places in cytogenetic perspective the problems arising in the consideration of transplantation specificity, actively acquired tolerance, and antibody synthesis as cellular phenotypes. If the analogies made with the ciliate work are valid, the repercussions on other related phenomena need to be examined—for example, the relation between chromosome balance and transplantation specificity (Hauschka and Amos) or the attempt to study mutational changes at the H-2 locus in heterozygous tumors, made by Klein (*47*), which finds a challenging parallel in the instability of certain serotypes in heterozygotes, noted by Sonneborn *et al.* (*48*). We are now in the difficult terrain between mutation (in which for the moment such phenomena as transduction may be included) and the types of nuclear differentiation just beginning to be explored, and already mentioned. Desirable experiments are many, focusing on the exploration of antigenic changes in cells cultured under defined conditions, excluding selection effects, and exploring the range of phenotypes possible for a given genotype. These experiments are easier to list than to carry out but at the present state of the art not impossible (*49*).

Summary

The paradoxical features of transplantation specificity—its strict genetic control in transfers of tissue from strain to strain as compared with its malleability on tissue passage in foreign immunological environments where the host does not reject the implant (F_1 hybrid passage, tolerance actively acquired by immature hosts, and so on)—present a challenge to genetic interpretation. The attempt is made in this article to show parallels between this behavior and such changes as the transformation of serotypes in *Paramecium,* in which the activity of genetic units becomes fixed as a cytoplasmic state—a cellular heredity persistent under specified environmental conditions but capable of change to an alternative state—while the genetic structure of the cell remains constant. The reactions appear to differ from those in the *Paramecium* case in that the diverse loci control a mosaic of different specificities, which change relatively independently of each other, in contrast to mutual exclusion of cytoplasmic states influenced by the different loci in *Paramecium.*

The process of antibody formation is considered as a change in cellular phenotype from the same point of view. The primary response in the stem cells of the lymphoid tissues is interpretable as the establishment of a new cytoplasmic state in response to a nuclear stimulus by the foreign antigen. For the secondary response, the suggestion is made that a reaction of antigen with cellular antibody at the surface of stem cells exhibiting the primary response serves as the stimulus for specific proliferation of antibody-forming clones of cells. A parallel is drawn with the fertilization reaction, specifically with regard to the initiation of cleavage in eggs by antisera to them.

Finally, a general chromosomal mechanism is sought for these phenomena, on the basis of activities of specific chromosome regions in response to special developmental stimuli, such as the disproportionate local synthesis of deoxyribonucleic acid demonstrated in the giant chromosomes of the Diptera. By a correlation of such activities with the nucleocytoplasmic system of ribonucleic acid granules on membranes, a possible mechanism appears for the formation, in response to environmental stimuli, of cytoplasmic states which might supply the persistent pattern required for this type of cell heredity. The analogies made, it is believed, provide a framework for the design of test experiments.

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CURRENT PROBLEMS IN RESEARCH

Thermoelectricity at Very Low Temperatures

Kelvin's discovery may be the key today to electron transport problems.

D. K. C. MacDonald

The experimental discovery of thermoelectricity dates from early in the last century. The Seebeck potential, or thermoelectric force, is the voltage produced in a circuit of two dissimilar elements when one junction is heated relative to the other (Fig. 1). The Peltier heat is the component of heat evolved or absorbed at the junctions per unit time when unit current flows in a circuit. It was William Thomson (Lord Kelvin), however, who in 1854 essayed a thermodynamic analysis of these effects (*1*), recognizing that they must be interrelated, and who was then led to make the remarkable prediction that a third effect (known today as the Thomson heat) must exist in a single conductor when a current flows through it and the conductor is in a temperature gradient. The Thomson heat is reversible in the sense that a component of heat is evolved or absorbed, depending on the relative direction of the electric current and temperature gradient. After his theoretical prediction, Thomson then went on to show the existence of this effect by a painstaking series of experiments. The definition of the Thomson coefficient μ is given by the following equation:

$$\dot{Q} = -\mu J_x \frac{dT}{dx} + \frac{J_x^2}{\sigma} \qquad (1)$$

where $\dot{Q}$ is the heat evolved per unit volume per unit time in a conductor; J_x is the current density; dT/dx is the temperature gradient; and σ is the electrical conductivity.

The second term in Eq. 1 corresponds to the *irreversible* Joule heating, and it

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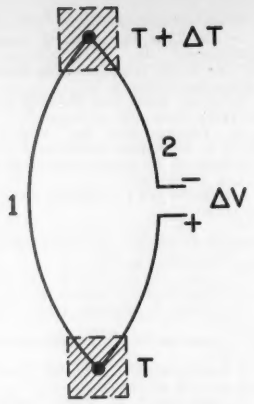

Fig. 1. Schematic thermoelectric circuit. The net thermoelectric power of this circuit is given by $dV/dT = S_1 - S_2$, where S_1 and S_2 are the absolute thermoelectric powers of conductors No. 1 and 2. If $S_1 > S_2$, then the polarity of ΔV is as shown in the figure.

is assumed that the Thomson heat and the Joule heat are independent of one another. It is clear that the Thomson heat (μ), like the electrical conductivity (σ) [or thermal conductivity (κ)], is a bulk property of a conductor, and so indeed are the Peltier heat and absolute thermoelectric power; unfortunately, confusion still sometimes occurs today when it is implied that the Peltier heat and thermoelectric power are "contact" phenomena because they have to be *measured* in a circuit composed of two different conductors.

The thermoelectric power is of great practical significance, since of course the use of thermocouples as thermometers depends on the very existence of this effect. On the other hand, we might perhaps say that thermoelectricity, until rather recently, has been to some extent the "Cinderella" of conduction phenomena from the point of view of yielding fundamental information about electron-transport behavior. In particular, in the last 30 years, a great deal of work has been done on the investigation of electrical conductivity at low temperatures (by which, roughly, we mean liquid-hydrogen temperatures—say, 20°K and below), and since World War II this work has grown to be very intensive at temperatures down to those of liquid helium (say, 1.5° to 4°K). Also, during this period *thermal* conductivity has become a rapidly growing field of interest. However, both of these parameters essentially measure thermodynamically irreversible effects. As a consequence of this, at sufficiently low temperatures (typically, below 4°K in a pure metal) the irreversible scattering of electrons by chemical impurities and physical defects in the lattice tends to dominate the situation, and it quickly becomes more and more difficult to extract information about the scattering of electrons by thermally activated processes. Of recent years, this has been seen to be particularly unfortunate because the details of thermal scattering of electrons are of great interest to the fundamental theory at these low temperatures. In addition, however, when more than one type of scattering process is involved, each, acting independently, would have to contribute a positive resistivity, since we are dealing with irreversible processes; put in other words, scattering due to physical defects, chemical impurities, excited lattice waves ("phonons") of high energy, low-energy phonons, or other causes must in each case be essentially positive, and it is not always easy to distinguish experimentally between these types with certainty. Lastly, the resistivities being essentially irreversible effects, little can be said about their expected behavior from a thermodynamic point of view (except, as we have said, that electrical and thermal resistivity must indeed be positive.)

Not so, however, for the thermoelectric effects. It is becoming clear that the puzzling changes of sign observed in some elements, as we vary the temperature, may well be a direct consequence of the changing predominance of different scattering components. It is indeed still true that the thermoelectric power (or Thomson heat) is sensitively dependent, in an almost alarming way in some cases, on temperature, on the type of im-

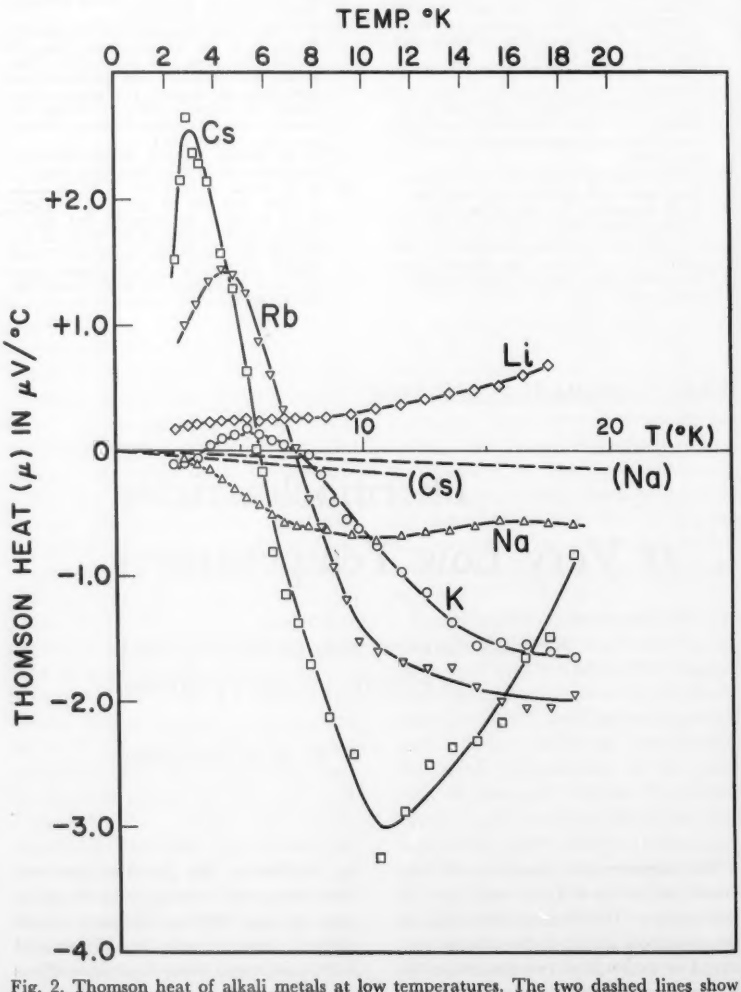

Fig. 2. Thomson heat of alkali metals at low temperatures. The two dashed lines show the detailed predictions of theory at low temperatures, ignoring phonon-drag; A. H. Wilson (*13*) gives $\mu = \pi^2 kT/3eT_0$ (compare Eq. 4 in text). [After MacDonald, Pearson, and Templeton (*14*)]

purity present, and so on, but this very sensitivity appears now to offer thermoelectricity as a rather valuable parameter for testing theories of conduction and for obtaining fresh information in this field. At the same time, it is a consequence of the *reversibility* of the thermoelectric phenomena that the behavior is not necessarily limited at low temperatures by the irreversible scattering due to impurities and the like, in the way that the electric and thermal resistivities are. Finally, we can, in some cases, usefully appeal to the laws of thermodynamics for some guidance as to what behavior we must expect from the thermoelectric coefficients.

Let us turn, then, to consider the significance of recent experimental work on thermoelectricity at low temperatures—say, 20°K and below.

Thomson Heat and Thermoelectric Power

William Thomson himself first suggested that the Thomson heat might be regarded essentially as the specific heat of electricity. This is not, however, to be identified immediately with the familiar specific heat at constant pressure or constant volume; it is a rather special specific heat, measured in a temperature gradient under conditions of no net electric current. Now in order to evaluate this properly we must appeal to some detailed theory of electron transport, but it would certainly be reasonable to assume that the Thomson heat should be fairly close in value to the more conventional equilibrium electronic specific heat. Thus, we should expect

$$\mu \sim C \qquad (2a)$$

or

$$\mu \sim c_{el}/e \qquad (2b)$$

where C is the specific heat per unit (free) charge transported [assumed positive from the defining Eq. *1*]; c_{el} is the specific heat per electron; and e is the charge of an electron in sign and magnitude. The relation shown in Eq. 2b follows from Eq. 2a of course if we assume conduction by free electrons. Now, the modern theory of metals gives

$$c_{el} = \frac{\pi^2 k}{2}\left(\frac{T}{T_o}\right) \qquad (3)$$

where T_o is the electron-degeneracy temperature (around 50,000°K for a typical metal), and thus we might expect

$$\mu \sim \frac{k}{e}\left(\frac{T}{T_o}\right) \qquad (4)$$

Now k/e is about 10^{-4} volt/°C and we should therefore expect a Thomson heat falling linearly with temperature and diminishing from about 10^{-7} volt/C° in the region below about 20°K. Actually, one usually measures the absolute thermoelectric power (S) of a metal, but since we have the Thomson relation

$$\mu = \frac{T\,dS}{dT} \qquad (5)$$

μ and S should be identical if Eq. 4 is valid. Actually, few metals seem to be "well-behaved"—at first glance, anyway—in this temperature region. Perhaps most striking are the Thomson heats of the alkali metals between 2°K and 20°K, shown in Fig. 2. The variation of thermoelectric behavior with temperature in most of this group of metals appears rather disconcerting, and the magnitudes of the Thomson heat and thermoelectric power, particularly in the heavier alkali metals, are often greatly in excess of the predicted values as indicated by the relation of Eq. 4 above.

"Phonon-drag Effect"

The tentative theoretical explanation today of these results rests on the so-called "phonon-drag" effect [or Gurevich effect (*2*)]. When we think of the Thomson heat as a specific heat of electricity, we are confining our attention essentially to the thermal entropy of the conduction electrons themselves. That is to say, under a temperature gradient, we may expect that the "hot" electrons (since they have higher velocities, for one thing) will tend to drift more rapidly towards the "cold" end than the "cold" electrons will drift in the opposite direction, and that this will give rise to a thermoelectric current. However, if we also recall that the electrons collide with the excited lattice waves (or "phonons"), it is not difficult to see that we may be able, in this way, to "tap" the entropy gradient of the lattice waves as well. Perhaps the simplest way to think of this process is as follows: When a temperature gradient is present, the phonons will themselves carry a thermal current (the lattice heat flow) and if phonon-electron collisions are important—as indeed they are in a pure metal at low temperatures—then the phonons may tend to "drag" the conduction electrons with them from hot to cold. Thus arises the "phonon drag" effect, producing an additional component of thermoelectric power.

A simple momentum argument (see, for example, *3*) leads us to expect:

$$S \sim \alpha C_{latt}/N_{el} \qquad (6)$$

where C_{latt} is the lattice specific heat per unit volume; N_{el} is the density of

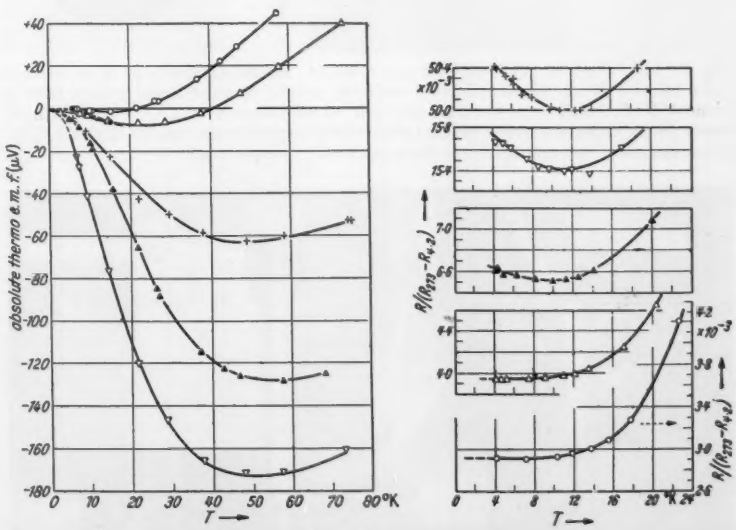

Fig. 3. (Left) Absolute thermoelectric force of copper and alloys. (Open circles) Pure Cu; (open triangles) pure Cu + 0.0009 atomic percent Sn; (solid triangles) pure Cu + 0.0026 atomic percent Sn; (open triangles, inverted) pure Cu + 0.0054 atomic percent Sn; (plus signs) pure Cu + 0.026 atomic percent Sn. (Right) Relative electrical resistance of these copper and copper-tin alloys. [After MacDonald and Pearson (*6*)]

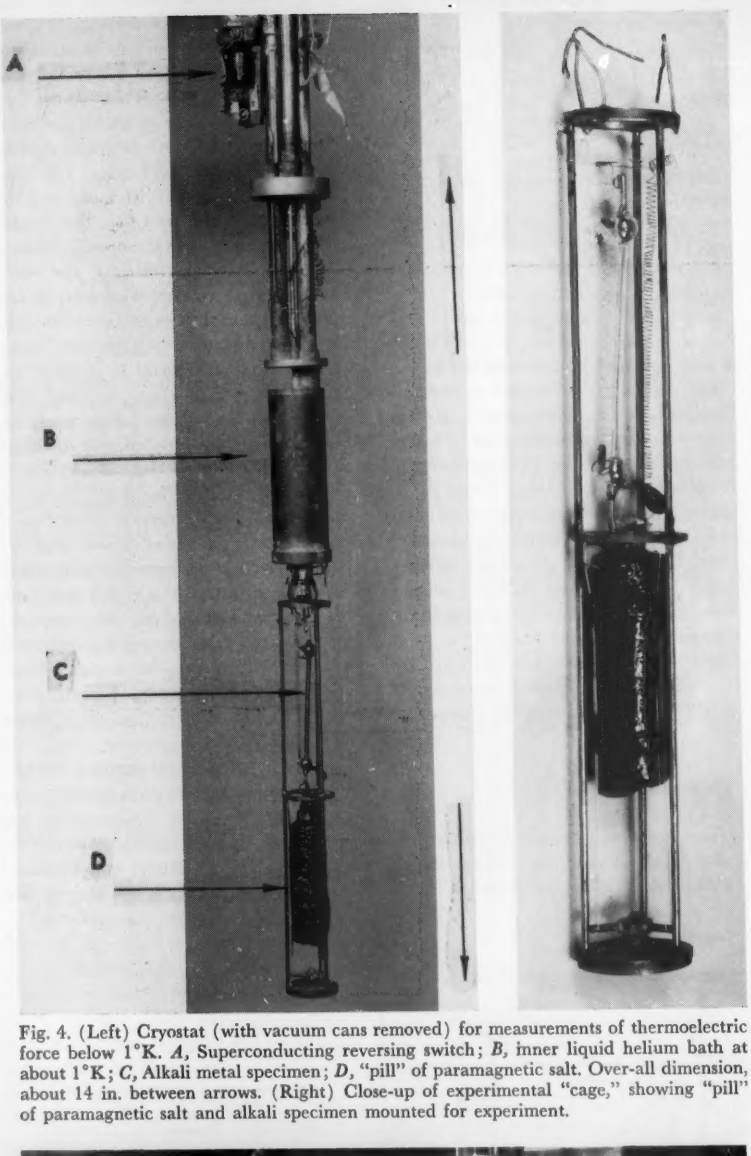

Fig. 4. (Left) Cryostat (with vacuum cans removed) for measurements of thermoelectric force below 1°K. *A*, Superconducting reversing switch; *B*, inner liquid helium bath at about 1°K; *C*, Alkali metal specimen; *D*, "pill" of paramagnetic salt. Over-all dimension, about 14 in. between arrows. (Right) Close-up of experimental "cage," showing "pill" of paramagnetic salt and alkali specimen mounted for experiment.

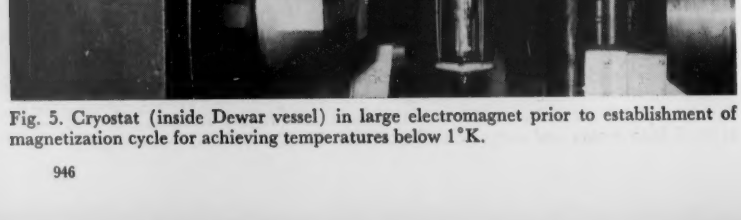

Fig. 5. Cryostat (inside Dewar vessel) in large electromagnet prior to establishment of magnetization cycle for achieving temperatures below 1°K.

free electrons; and α is a parameter lying between 0 and 1; if phonon-electron collisions can be neglected, $\alpha = 0$, while if phonon-electron collisions are dominant, $\alpha \rightarrow 1$.

As the temperature increases, the lattice specific heat grows rapidly [with $(T/\Theta)^3$], and so long as α remains significant, Eq. 6 can give rise to quite a large amount of thermoelectric power. More detailed theories, such as J. M. Ziman and M. Bailyn are now developing, suggest that the behavior of the "phonon-drag" effect could be quite complicated, depending on the precise mechanisms of phonon-electron scattering. Now scattering may take place by direct interchange of momentum between a phonon and an electron (the so-called "normal" process), or the exchange may also involve momentum corresponding to one of the reciprocal lattice vectors. It seems that this latter so-called "Umklapp process" (*4*) may yield a component of thermoelectric power opposite in sign to a component due to "normal" processes; furthermore, the relative proportion of these two scattering mechanisms may depend quite sensitively on the temperature. It then appears quite possible that a satisfactory explanation for the behavior of thermoelectric power down to, say, liquid helium temperatures may be provided in this way; indeed Ziman has suggested that this may well be one of the most sensitive ways of estimating the shape of the electron Fermi surface in relation to the Brillouin zones, since this is a vital factor in determining the relative frequency of the Umklapp processes.

Anomalous Minimum of Electrical Resistance

At the same time, we should not forget many other peculiar features found in thermoelectric power in the liquid helium and hydrogen temperature region. It has been known for some time (see, for example, *5*, *6*) that in metals such as copper, very small amounts of impurity (of the order of 0.1 atomic percent) can have a quite violent effect on the thermoelectric power in this region, and it appears rather certain that this behavior is related quite closely to the appearance of an anomalous minimum in the electric resistance of such metals at low temperatures. This is illustrated in Fig. 3. The anomalous minimum of electrical resistance has excited growing interest since it was first discov-

ered in experiments on gold at Leiden (*7*), but so far no adequate theoretical explanation has been found for this behavior. One is sometimes tempted to suspect that the fundamental explanation, when found, might perhaps be comparable in significance for electron transport theory to the explanation of superconductivity—although the phenomenon is of course less dramatic.

Measurements Below 1°K

Since experiments have proved so fruitful down to liquid-helium temperatures, one is naturally led to extend the work to even lower temperatures. Some results below 1°K have now been published (*8, 9*); apparatus for use in experiments at these temperatures is shown in Figs. 4 and 5. Since the "phonon-drag" effect should diminish as T^3 (compare Eq. 6) while the purely electronic component should diminish only with T (see Eq. 4), we should certainly expect that at sufficiently low temperatures Eq. 4 would become essentially valid—and, in fact, temperatures below 1°K, as a general rule, ought to be sufficient to achieve this. We have now carried out initial experiments on the alkali metals; on copper, silver, and gold; and on one or two other metals, such as platinum, nickel, and iron. In the alkalis we find that the thermoelectric power has indeed now fallen to the order of magnitude predicted by Eq. 4—that is, to around 10^{-8} to 10^{-9} volt/°C in the region below 1°K. On the other hand, the temperature-dependence is not always linear, as we might expect it to be; indeed, in the case of potassium (compare the two parts of Fig. 6) the temperature-dependence appears almost quadratic, and, so far, we can offer no theoretical explanation for this behavior. Much remains to be done here, even among the alkali metals; in particular the dependence of thermoelectric power on impurity requires careful investigation.

Perhaps the most striking results below 1°K are those for copper, silver, gold, and platinum—particularly those obtained on gold. Figure 7 shows experimental data on two samples of gold—one specimen very much purer than the other—and Fig. 8 shows some experimental results on silver. The most remarkable feature is the high order of magnitude of the thermoelectric power in gold, even at 0.5°K. At this temperature the "phonon-drag" effect should be quite negligible, and for the ordinary electronic component we should expect a thermoelectric power of about -4×10^{-9} volt/°C; actually, with the purer gold specimen, a figure about 1000 times greater (about -4 μv/°C) is observed! Again, no theoretical explanation for this remarkable behavior is yet forthcoming; naturally we are most interested to see whether any other metals or group of metals will show thermoelectric powers of this (or perhaps an even greater) order of magnitude.

The very high thermoelectric power found in gold at these low temperatures makes one consider another question. A thermoelectric power of about 10^{-8} volt/°C, which we might generally expect at 1°K, corresponds to an entropy of about 2×10^{-4} cal/°C per mole of electrons transported (that is, 1 faraday—about 10^5 coul of charge transported). On the other hand, a thermoelectric power as large as 5 μv/°C corresponds to about 0.1 cal/°C Faraday. This suggests at least the possibility of thermoelectric cooling even at these very low temperatures.

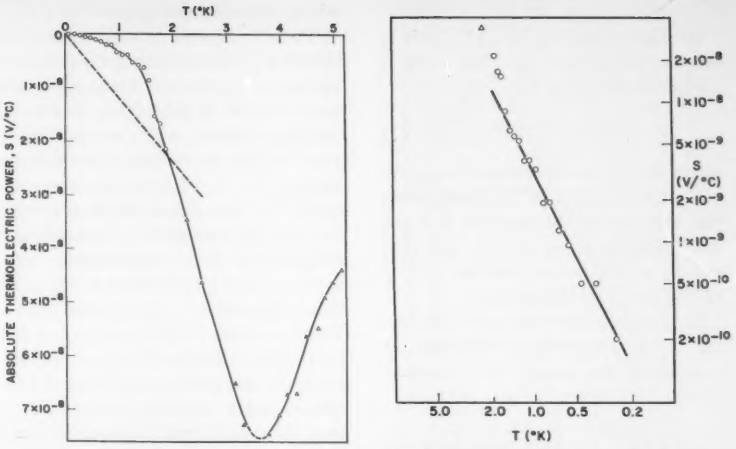

Fig. 6. (Left) The dashed line shows the predicted behavior at very low temperatures (irrespective of phonon-drag); Wilson (*13*) gives $S=\pi^2kT/3\epsilon T_0$. (Right) Data replotted on logarithmic scales; line shows T^3 dependence. [After MacDonald, Pearson, and Templeton (*8*)]

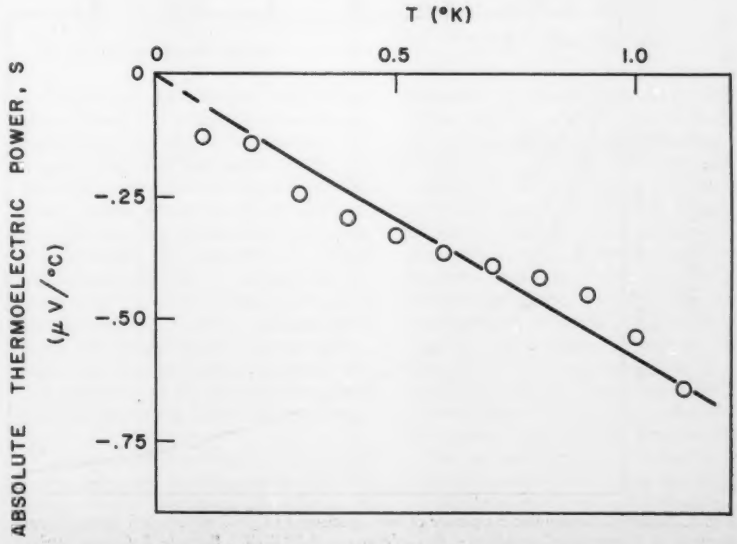

Fig. 7. Absolute thermoelectric power of silver at very low temperatures. [From data of MacDonald, Pearson, and Templeton]

Ideal Limit of Refrigeration

A detailed analysis (see *10*) leads to the conclusion that the ideal limit of refrigeration is given by

$$\Delta T/T_o = S_o^2/2L_o \qquad (7)$$

where ΔT is the reduction of temperature obtained; T_o is the low temperature (the cold end of the couple); S_o is the thermoelectric power at the cold end; and L_o is the Lorenz number ($L = \kappa/\sigma T$) at the low temperature.

For a metal whose conductivity is limited by impurity or defect scattering (as is generally the case at low temperatures)

$$L_o = \frac{\pi^2}{3}\left(\frac{k}{e}\right)^2 \approx 2.5 \times 10^{-8}\ (\text{volt/deg})^2 \qquad (8)$$

If, now, $S_o \approx 10^{-3}$ volt/°C, then evidently, from Eq. 7, the outlook is quite hopeless for thermoelectric cooling! In the case of gold, setting $S_o \approx -5 \times 10^{-6}$ volt/°C, we would expect $\Delta T/T_o \approx 5 \times 10^{-4}$ at temperatures around 1°K—an amount which of course is still far too small to be practically useful. However, at our present state of knowledge we cannot be sure that a metal or alloy is not to be found with even higher thermoelectric power at low temperatures, and if one could be found for which S_o was perhaps 10^{-4} volt/°C, the situation would become very promising. This naturally provides a further incentive for experimental work on thermoelectricity at low temperatures.

There is another hopeful aspect; the data of Fig. 8 show that the largest thermoelectric power was obtained in the purer sample of gold. Now, if a metal could be obtained which was sufficiently pure so that the conductivity was not limited, at the low temperatures required, by impurity or defect scattering but was limited rather by thermal scattering, then the Lorenz number (L) could in principle be very much lower than the limiting value quoted above. This is because, if electrons are scattered by thermal vibrations at low temperatures, the electrical conductivity (σ) increases much more rapidly (as T^{-5}) than does the thermal conductivity (κ) (which increases as T^{-2}). Thus it is at least possible that a metal might be obtained which would be sufficiently pure to have both a high enough value of S and a low enough value of L to be of use for low-temperature refrigeration.

If thermoelectric refrigeration could be made a practical possibility at low temperatures (say 1°K), it would be of considerable benefit to experimental research. At present the only feasible method is to use the adiabatic demagnetization of a suitable paramagnetic salt, as first envisaged by Debye and Giauque, in order to achieve temperatures below 1°K. A number of such salts are available—such as iron ammonium alum (which is rather popular), with which one can conveniently work down to about 0.05°K, and, say, cerium magnesium nitrate, with which temperatures of a few millidegrees Kelvin can be reached. Of course such salts are used as refrigerating agents in this work, but there are certain serious difficulties that are met with. As the temperature is reduced, the thermal conductivity of the salts themselves becomes rather poor, and the temperature distribution may thus become rather inhomogeneous through the salt "pill." It is also not easy to achieve satisfactory thermal contact with the salt itself for the purpose of cooling some other material; my coworkers and I usually use the method of recrystallizing the salt directly from a saturated solution onto a silver mesh, but we are by no means certain of the adequacy of thermal contact below, say, 0.1°K.

Another problem of long standing is the question of determining the absolute temperature below 1°K. An approximate temperature is obtained by assuming that the magnetic susceptibility of the salt (χ) obeys Curie's law ($\chi \propto 1/T$). This is in fact an excellent approximation in the liquid-helium region; hence a calibration of magnetic susceptibility against absolute temperature can readily be made in this temperature range. This calibration is then extrapolated to provide a so-called "Curie temperature" down to the low temperatures achieved when the salt is adiabatically demagnetized. However, deviations from Curie's

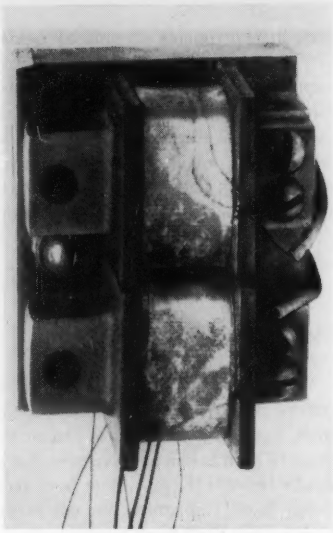

Fig. 9. Superconducting reversing switch designed by Templeton for operation in liquid helium. (About 1½ by 1¼ in.; height, about ¾ in.)

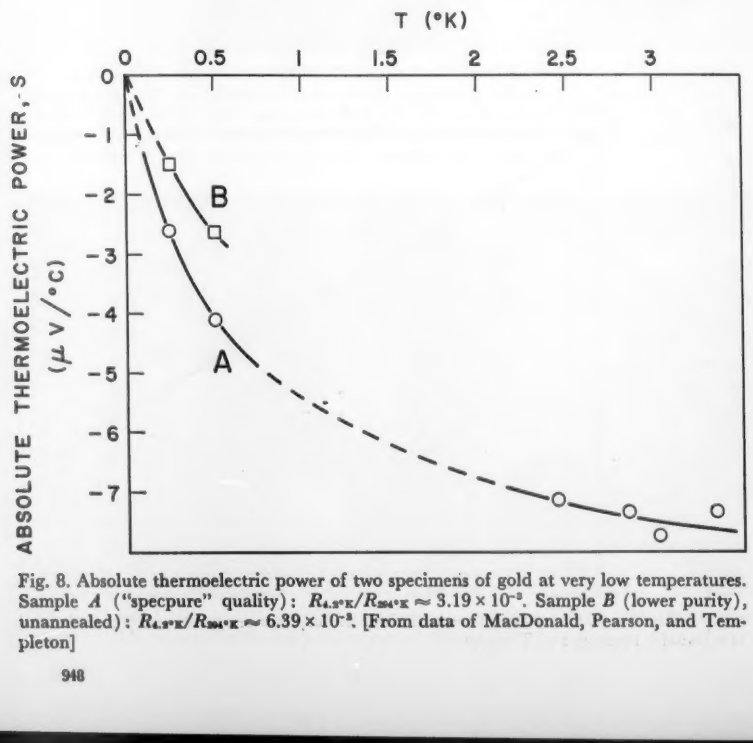

Fig. 8. Absolute thermoelectric power of two specimens of gold at very low temperatures. Sample *A* ("specpure" quality): $R_{4.2°K}/R_{294°K} \approx 3.19 \times 10^{-3}$. Sample *B* (lower purity, unannealed): $R_{4.2°K}/R_{294°K} \approx 6.39 \times 10^{-3}$. [From data of MacDonald, Pearson, and Templeton]

law must (and indeed do!) occur at sufficiently low temperatures, and thus for accurate work it is necessary to make an absolute calibration in the very low temperature region. This, in principle, can be done by various methods involving the second law of thermodynamics, by taking the salt through a reversible cycle. However, a difficulty arises in the fact that the calibration found does not always agree from laboratory to laboratory, or indeed necessarily from one sample of a salt to another, since the behavior may depend on the previous history of the specimen. One solution is to use as a thermometer an auxiliary sample of a paramagnetic salt (such as cerium magnesium nitrate) which is known to obey Curie's law down to rather low temperatures, but of course this all adds to the experimental difficulties involved. In principle, a very attractive solution would be one in which use was made of the electrical Brownian movement ("thermal noise") in a resistor for thermometry, but there are many difficult technical problems as yet unsolved, not the least of which is that of measuring the very small noise voltage with some accuracy.

Another challenging aspect of the measurement of thermoelectric power at very low temperatures is the problem of measuring the small thermoelectric voltages involved in many cases. The superconducting reversing switch (see Fig. 9) and superconducting modulator developed in these laboratories by Templeton (*11*) have proved invaluable, and we feel that the limit of sensitivity has by no means yet been reached (*12*). All in all, it appears that the study of thermoelectricity at very low temperatures is full of promise, and "Cinderella" may yet turn out to be the "belle of the ball."

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News of Science

White House Reports on Scientific Aspects of Radiation Belts Created by Argus Experiments

Three nuclear test explosions, in a series called Project Argus, were set off 300 miles above the earth on 27 and 30 August and 6 September 1958 by a Navy task force in the South Atlantic Ocean. These tests, the first such explosions in outer space, are reported to have had a force measured in kilotons.

Argus was first announced by the New York Times *on 19 March. The announcement was promptly confirmed by the Department of Defense, but Deputy Secretary of Defense Donald Quarles, speaking at a news conference, was reluctant to go into any details and expressed regret that the project had been made public. On 25 March the White House released a report on the Argus experiments prepared under the direction of the President's Science Advisory Committee and the International Geophysical Year Committee of the National Academy of Sciences. The text of the report follows.*

Committee's Report

This report discusses the scientific as distinct from the military results and implication of the Argus experiments. Because of the fact that many of the experiments performed in connection with these atomic bursts involved both the election trapping phenomenon and classified military effects phenomena, it was considered advisable to withhold all results classified until a proper sorting of the information could be accomplished. Since reports on relevant military aspects have only become available within the last two weeks, it has not heretofore been possible to release any of this information.

The scientific aspects of these experiments, involving three high-altitude small atomic bursts over the South Atlantic in August–September 1958 are regarded by many participants as one of the major achievements of the International Geophysical Year. The execution of these experiments engaged the coordinated resources of large segments of the scientific talent of the nation, and it was apparent that the effects of the experiment, if successful, would be recorded by instruments of the far-flung international network of the IGY. The compilation of the observational and interpretative contributions by the many participants will doubtless stand as a durable milestone in the development of man's knowledge of the great natural phenomena of the earth's atmosphere which have engaged his study for many centuries.

Christofilos Proposal

The underlying idea for the Argus experiments was due to Nicholas C. Christofilos, physicist of the Lawrence Radiation Laboratories of the University of California. In October 1957 he called attention to the fascinating physical effects which might be expected to follow an atomic burst in the near-vacuum of outer space, high above the earth and its dense atmosphere. Of the various effects contemplated, the most interesting one promised to be the temporary trapping of high-energy electrons at high altitudes in the magnetic field of the earth. Following the burst there would be thrown off in all directions nuclei of intermediate atomic weight. Most of these nuclei, as is well known, are radioactive and subsequently decay with the release of energetic electrons and gamma rays. Most of the decays occur within a few minutes. The fission fragments themselves are electrically charged and move

at high velocity. Hence, their paths in the near-vacuum conditions of outer space would be controlled, in the main, by the earth's magnetic field and would be helical ones around magnetic lines of force. The electrons resulting from their decay would likewise move in helical paths in the magnetic field. In accordance with the theory of such motion, which has been known and demonstrated on a laboratory scale for many years, it could be expected that these high-energy electrons would be trapped in the outer reaches of the earth's magnetic field and would only slowly "leak" down into the atmosphere and be lost due to collisions with air molecules in the tenuous upper atmosphere. The trapping region would be in the form of a thin "magnetic shell" encircling the earth and bounded by lines of force. Trapping times ranging from minutes to weeks were estimated for electrons whose helical paths ranged as close to the solid earth as 100 to 2000 miles, respectively.

Idea Was Studied

The proposal of Christofilos captured the imagination of a number of other scientists and the idea was studied intensively during the following months.

Meanwhile, the United States had succeeded in launching its first IGY satellite, Explorer I, which had as its primary purpose the study of cosmic radiation in the vicinity of the earth. The observations with this satellite as well as those with Explorer III, launched soon afterwards, led to the discovery of a major new phenomenon—namely, the existence in the region around the earth of a belt of high-intensity corpuscular radiation due to natural geophysical causes.

The first public report of this discovery and of its interpretation in terms of magnetic trapping was made on May 1, 1958, at an IGY symposium of the National Academy of Sciences and the American Physical Society. The report was given by James A. Van Allen, who with his colleagues of the State University of Iowa had planned and carried out the experiments.

The existence of the natural, trapped radiation served as an over-all validation of the proposal of Christofilos. At the same time it posed the problem of whether observation of the effects of an artificial injection of electrons would be possible in the presence of the natural "background."

Initiation of Argus Experiment

The fate of the entire enterprise was laid before the President's Science Advisory Committee, since it was clear that the undertaking involved a mixture of scientific and military interest. At the suggestion of the President's Science Advisory Committee, a group of representatives of the scientific community and the defense community were brought together to appraise all aspects of the matter. It was decided in late April 1958 to proceed with the Argus experiments as a major national undertaking. The operational and technological management of the project was vested in the Advanced Research Projects Agency of the Department of Defense. In his capacity of chief scientist, Herbert York, directed the program for that agency.

The Air Force Special Weapons Center undertook the preparation of a series of high-altitude sounding rockets for the study of the lower fringes of the expected effect at altitudes of about 500 miles, utilizing a five-stage solid propellant rocket vehicle that had been developed by the NACA. The Air Force Cambridge Research Center and the Stanford Research Institute developed, located, and prepared to operate a variety of equipment at suitable ground stations and aboard aircraft and ships. The difficult mission of delivering three small-yield atomic devices to high altitude and detonating them there at a pre-chosen location over the South Atlantic Ocean was undertaken by a Navy task force specially organized for the purpose.

Explorer IV

Meanwhile, the Academy's IGY group was planning to pursue vigorously further studies of the Van Allen radiation belts, initially revealed by Explorers I and III. To secure more detailed knowledge of the Van Allen radiation belts, and to observe any artificial phenomenon from the proposed Argus experiment, instrumentation was accordingly designed and developed at the State University of Iowa. Jupiter C rockets of the type developed by the Army Ballistic Missile Agency and the Jet Propulsion Laboratory of the California Institute of Technology had already been scheduled as satellite vehicles. The result of this program was the launching of Explorer IV.

Conduct of Argus Experiment

On July 27, 1958, Explorer IV was successfully placed in an orbit inclined at a 51-degree angle with the equator and, with all equipment operating perfectly, immediately began transmitting valuable new information on the nature, intensity, and distribution of the natural radiation. The high inclination orbit proved to be a distinct advantage over the previously used 34-degree inclination orbits due to its much greater spatial coverage. Meanwhile the new observing stations were being set up and the Navy task force was en route to the designated area of the South Atlantic. Preliminary sounding rocket flights were being conducted at Wallops Island in Virginia, Ramey Air Force Base in Puerto Rico, and Patrick Air Force Base in Florida.

Bursts occurred on the 27th and 30th of August in the early morning hours and on the 6th of September shortly before midnight, Greenwich time. In order to produce an electron shell having quantitative significance, it was desirable to minimize the loss of electrons to the atmosphere, and calculations showed that this could best be done by placing the source of the shell between longitude 0° and longitude 30° W. This follows from the fact that the earth's magnetic axis is tilted and displaced with respect to its rotational axis, so that the edges of the shell would come closest to the surface at these longitudes. The approximate latitude was 45° S.

Because of the small yields involved and the high altitude of the bursts there was no fallout hazard.

Aurora Followed Blast

A fascinating sequence of observations was obtained. The brilliant initial flash of the burst was succeeded by a fainter but persistent auroral luminescence in the atmosphere extending upward and downward along the magnetic line of force through the burst point. Almost simultaneously at the point where this line of force returns to the earth's atmosphere in the Northern Hemisphere—the so-called conjugate point—near the Azores Islands, a bright auroral glow appeared in the sky and was observed from aircraft previously stationed there in anticipation of the event, and the complex series of recordings began. For the first time in history, measurements of geophysical phenomena on a worldwide scale were being related to a quantitatively known cause—namely, the injection into the earth's magnetic field of a known quantity of electrons of known energies at a known position at a known time.

The diverse radiation instruments in Explorer IV recorded and reported to ground stations the absolute intensity and position of this shell of high-energy electrons on its passes through the shell shortly after the bursts. The satellite continued to lace back and forth through the man-made shell of trapped radiation hour after hour and day after day. The physical shape and position of the shell were accurately plotted out and the decay of intensity was observed. Moreover, the angular distribution of the radiation was measured at each point. The shape and form of a selected magnetic shell of the earth's magnetic field was being plotted out for the first time by experimental means.

Rocket Soundings Made

In their helical excursions within this shell the trapped electrons were traveling vast distances and were following the magnetic field pattern out to altitudes of

over 4000 miles. The rate of decay of electron density as a function of altitude provided new information on the density of the remote upper atmosphere, since atmospheric scattering was the dominant mechanism for loss of particles. Moreover, continuing observation of the thickness of the shell served to answer the vital question as to the rate of diffusion of trapped particles transverse to the shell. All of these matters were of essential importance in a thorough understanding of the dynamics of the natural radiation and were now the subject of direct study by means of the "labeled" electrons released from Argus I.

Throughout the testing period the planned series of firings of high-altitude sounding rockets was carried out with full success and with valuable results in the lower fringes of the trapping region.

Explorer IV continued to observe the artificially injected electrons from the Argus tests, making some 250 transits of the shell, until exhaustion of its batteries in late September, though by that time the intensity had become barely observable above the background of natural radiation at the altitudes covered by the orbit of this satellite.

It appears likely, however, that the deep space probe, Pioneer III, detected a small residuum of the Argus effect at very high altitudes on December 6, 1958. But the effect appears to have become unobservable before the flight of Pioneer IV on March 3, 1959.

The site of the Argus tests was such as to place the artificially injected radiation shell in a region where the intensity of the natural radiation had a relative minimum. If the bursts had been produced at either higher or lower latitudes, the effects would have been much more difficult to detect, plot, and follow reliably for long times after the blasts.

The immense body of observations has been under study and interpretation by a large number of persons for about seven months. Only now are satisfactory accounts becoming available from the participating scientists. From these observations we have learned, to cite by two examples: (i) There was no diffusion of electrons transverse to the electron shell since the thickness of the shell remained constant. Also traces of the shell persisted for many days and possibly weeks; (ii) Extrapolations of the earth's magnetic field into space, which have been based on surface measurements, were confirmed by the experiment. The experiment has made it possible to predict the shape and intensity of the earth's field with considerable accuracy out to distances of the order of several earth's radii.

The directness and clarity of the artificial injection tests have provided a sound basis for interpretation of the natural radiation trapped around the earth. It is likely that many important contributions will continue to arise from the great diversity of geophysical observations being conducted by other countries participating in the International Geophysical Year.

The IGY group of the National Academy of Sciences planned, as with its other program, to make the scientific results of Explorer IV available as rapidly as analytical procedures permitted. In view of the progress made by experimenters and analysts, the academy took steps more than a week ago to arrange for a presentation of summary papers at its annual meeting on April 27–29, 1959.

IAEA Head Says Member Nations Fail to Give Full Support

W. Sterling Cole, director-general of the International Atomic Energy Agency, has urged that his agency be allowed to perform the functions for which it was established. He says that the failure of nuclear powers to cooperate fully with the IAEA is hampering development of the atoms-for-peace program.

Background Cited

In a stirring address before the American Association for the United Nations, which met in Washington in March, Cole pointed out that the measure of success of a U.N. specialized agency is not so much in the efficiency of management of the organization itself as in the extent to which the supporting governments will actually use the international channels provided. Cole reminded the audience that when President Eisenhower made his atoms-for-peace proposal to the United Nations in 1953 which led to the formation of the IAEA, the underlying idea was entirely new. Cole commented: "For the first time in history it was proposed that a tremendous force usable for war and destruction be dedicated to the benefit of mankind everywhere and that knowledge in the peaceful application of this new-found force be shared without favor or discrimination."

Cole emphasized that the IAEA "constitution" is a treaty-statute approved by more than 80 nations. The agency's constituent assembly is an annual general conference of the member states, now numbering 70. Its managing directorate is a 23-member board of governors carefully balanced to include representation of the atomic-industry nations, the material-supply nations, the recipient nations, and the several major geographic regions of the world. He pointed out further that the agency has a staff of outstandingly competent scientists, engineers, administrators, and diplomats made up of representatives of more than half the member states.

Recommendations Offered

Cole summarized his recommendations as follows.

"The first decision which must be made is clear and straightforward. It is simply the decision that, having created an international body for defined purposes in connection with atomic energy, the Agency should be supported not only with generous financial contributions—as has been the case of the United States—but fully and without qualification in its operational aspects. We can be only partially effective if some nations maintain parallel machinery to do the same thing as the Agency but subject to individual nation selection, manipulation and control.

"Once this decision has been made, and with determination to sustain it, the subsequent steps become equally clear and straightforward: to discontinue further bilaterals or multilaterals [agreements], to begin to place under Agency administration the health and safety and materials safeguard measures embodied in existing bilateral and multilateral agreements, to begin to channel all atomic foreign aid through the Agency, and to start work on the instrument which will make possible the registration and accounting control of the nuclear fuel materials."

The United States has 42 bilateral and multilateral agreements with 40 countries, and one with the city of West Berlin, to assist in the peaceful development of atomic energy. Some 45,000 kilograms of U-235 has been set aside in accordance with these cooperation agreements.

This country has made 5000 kilograms of U-235 available to the IAEA and has promised to match the allocations of other countries. So far the United Kingdom has pledged 20 kilograms of U-235; the U.S.S.R., 50 kilograms. In addition, Portugal will provide 100,000 kilograms of normal uranium concentrate. The first purchase of nuclear fuel by any country through truly international channels was completed on 24 March, when Japan signed an agreement with the IAEA to buy 3 tons of natural uranium, provided by Canada, to be used in a 10-megawatt research reactor.

Antarctic Science

Albert P. Crary reported recently on his 2½ years in Antarctica as deputy chief scientist of the United States–International Geophysical Year program of the National Academy of Sciences. Crary has just returned from an assignment that also involved serving as station scientific leader at Little America. From that station, he led two major journeys of scientific exploration, the second ending on 1 February 1959.

Great Distances Traveled

On these traverses, he covered a total of almost 3100 miles, an expanse of ice wider than the United States. Crary also led a 320-mile traverse in April 1958, which integrated his longer trips with traverses from Byrd and Ellsworth stations to give a continent-wide scientific picture of unprecedented scope. In all, U.S. traverses organized by Crary totalled 7500 miles, spanning Antarctica from the Weddell Sea to the Ross Ice Shelf and into the Victoria Land Plateau.

Crary's first major trek, from 24 October 1957 to 13 February 1958, covered 1450 miles of the Ross Ice Shelf. On the second journey, which began 15 October 1958, and lasted 108 days, Crary's party travelled 1629 miles.

Group Records Varied Findings

During the latter trip, the group climbed Skelton Glacier to a height of 7500 feet, placing markers which will lay the groundwork for the first accurate measurements of mass ice flow down the glacier. They worked their way up the glacier to the Victoria Land Plateau, and proceeded inland 400 miles on the plateau, finding ice 8000 to 9000 feet thick. Average annual temperature on the plateau was determined to be −55°F, almost as low as the −58°F average at the South Pole. This was found by measuring temperatures in bore holes drilled to depths of about 50 feet. At this level, temperatures are known to be about the same as the annual average at the surface.

Among their other findings was an ocean-bottom depth beneath the Ross Ice Shelf of about 4400 feet below sea level, at 79°06′S, 165°30′E. It was measured by seismic sounding.

Primary purposes of the most recent traverse were to determine the snow and ice characteristics and thickness on a line extending directly into the main Antarctic highlands and to study the Skelton Glacier and the transition from low-lying ice shelf to high plateau.

More than a dozen specific types of scientific observations were made by the party, which also included Charles R. Wilson, Washington, D.C., and Stephen L. Den Hartog, Concord, Mass., glaciologists; Lyle D. McGinnis, Kaukauna, Wis., seismologist; and Frank C. Layman, Pittsburgh, Pa., mechanic. Trevor Hatherton, chief scientist of the New Zealand Antarctic program, accompanied the party most of the way.

Methods and Equipment Used

They travelled in three Sno-Cats. The first of these tractor-type vehicles carried an electronic crevasse detector, navigation equipment, and radio. Another housed seismic, gravity, and magnetic equipment, while a third carried mess facilities. Three 2½-ton sleds were used to haul fuel and spares. The party was resupplied by ski-equipped aircraft from Navy Task Force 43, under the command of Admiral George Dufek, which provided extensive logistic support for IGY scientific activities.

Elevations of the surface along the traverse route were obtained by altimetry and transit levelling. Thickness of ice was determined by seismic reflection methods. Characteristics of rock under the ice were established by seismic refraction methods.

Primarily to obtain data on annual snow accumulation, observations were made to depths of 10 meters from shallow snow pits and bore holes. Snow hardness, grain size and shape, densities, and temperatures were noted.

Surface meteorological data were collected on temperature, pressure, wind speeds, wind direction, cloud cover, and cloud types.

Standard "station" stops were spaced at intervals of about 30 miles for snow-pit studies, seismic reflections, gravity and magnetic observations, and temperatures in 10-meter bore holes. Minor stations were made about every 5 miles for gravity and magnetic studies.

During the passage up the Skelton Glacier, the intervals were shortened to 5 and 2 miles for standard and minor stations respectively. In addition, three major stations were made at the foot and top of the Skelton Glacier and at the western end of the plateau line. There, seismic refractions were added, the drill holes were made to depths of 20 meters, and snow samples were taken for oxygen-isotope studies.

Britain's Department of Scientific and Industrial Research

Some years ago Great Britain decided to try financing its Department of Scientific and Industrial Research on a 5-year basis. The experiment, which was designed to meet the needs of long-term planning of research, has proved successful, and the government is continuing the system for another 5 years.

An outline of the second 5-year plan was presented in the House of Commons recently by Harmar Nicholls, parliamentary secretary to the Ministry of Works, speaking on behalf of the Lord President of the Council for Scientific and Industrial Research, Lord Hailsham, who is the minister responsible for the DSIR. As before, the financial provisions of the program are subject to the necessary funds being voted annually by Parliament and may be reviewed in the event of a marked change in the economic situation or of major changes in cost. Some of the chief features of the new plan follow.

The Plan

Expenditure on research by the DSIR will be nearly doubled in the next 5 years. For the period 1959–64, approximately £61 million will be made available to the department, compared with £36 million for the first period, which ends on 31 March 1959.

Expansion will continue steadily throughout the period, and for the year 1963–64 expenditure is expected to reach about £14 million. This figure does not include certain special items, the largest of which is the British contribution to the European Organization for Nuclear Research (CERN), which will continue to be financed outside the 5-year plan.

The largest expansion will take place in the field of scientific grants to the universities. Post graduate awards to students will be increased by about 10 percent each year until in 1963–64, it is hoped, some 3800 students will be receiving DSIR grants for research training. In the same year it is expected that DSIR support for special research in the research departments of universities will be operating on a scale of about £1¾ million per annum.

DSIR Laboratories

In support of additional research carried out in the department's own laboratories, expansion of staff at the rate of about 6 percent per annum—or approximately 30 percent over the 5 years—is included in the plan.

Grants to the research associations will also be increased to over £2 million per annum by the end of the period. At present there are 49 organizations in the DSIR scheme. The Council for Scientific and Industrial Research will continue its policy of encouraging industry to bear an increasing proportion of the total cost. It may be expected, therefore, that the actual expansion of the research association movement will be proportionately greater than the increase in government grants.

It has also been decided to devote much more attention and more money to insure that the results of scientific research are known and applied.

It is also proposed that the Ministry of Works increase its rate of expenditure on behalf of DSIR so as to provide buildings and equipment for the increased staff of DSIR laboratories.

U.N. Space Group

The first meeting of the United Nations Committee on the Peaceful Uses of Outer Space has tentatively been scheduled for the second half of April, according to the *New York Times*. The committee, which consists of 18 government representatives, was established by

the General Assembly last December. It has not met because of a Soviet boycott resulting from the complaint that the committee has a pro-Western majority.

It is reported that the committee will elect officers and request Secretary General Dag Hammarskjold to outline activities in the field of outer space that should be undertaken by the United Nations and other international organizations. The committee will probably not begin full-scale operation until the Soviet Union agrees to cooperate. The *Times* article suggests that the disagreement over Soviet participation in the work of the committee can be overcome either at a meeting of foreign ministers, now expected on 11 May, or at a subsequent meeting of heads of government.

The U.S.S.R. will not cooperate unless the committee's membership is changed, and Communist and neutralist members are given the same number of seats as Western members. This change can be made only by the Assembly, which will not begin its 1959 session until September. If the Soviet Union accepted a compromise on the committee's membership, to be submitted to the Assembly next fall, this would improve the chances of inducing neutralist members, in particular India and the United Arab Republic, to participate in the committee's work. For weeks the United States has been trying to persuade Western members of the committee to hold a meeting in March or April, regardless of the Soviet boycott.

News Briefs

The National Science Foundation has announced the establishment of an Office of Social Sciences, with Henry W. Riecken as its head. The foundation's support of basic social-science research began 5 years ago, but the work has previously been associated with the program in the natural sciences. An Advisory Committee for the Social Sciences was announced simultaneously. Members include: Leonard S. Cottrell, social psychologist, Russell Sage Foundation; Fred Eggan, professor of anthropology, University of Chicago; John Gardner, president, Social Science Research Council; Joseph Spengler, professor of economics, Duke University; S. S. Wilks, professor of mathematics, Princeton University; and Dael Wolfe, executive officer, AAAS.

* * *

An exhibition of material relating to Charles Darwin has opened at the University of Pennsylvania Museum. The exhibition, sponsored by the American Philosophical Society Library and the Friends of the University of Pennsylvania Library, commemorates the 100th anniversary of the publication of Darwin's *On the Origin of Species*. The exhibit includes the only known complete set in the United States of the first edition of *On the Origin of Species*, as well as subsequent revisions and reprints.

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The American Institute of Physics, which now publishes translations of six Soviet physics journals, is bringing out another important physics journal, *Uspekhi Fizicheskikh Nauk*. The new translation project is being supported by the National Science Foundation.

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Two AAAS affiliates, the American Society of Heating and Air-Conditioning Engineers and the American Society of Refrigerating Engineers, have merged to form the American Society of Heating, Refrigerating, and Air-Conditioning Engineers. The consolidated society has a membership of more than 18,000. Cecil Boling of West Hartford, Conn., is president.

Grants, Fellowships, and Awards

Fulbright and Smith-Mundt awards. For American applicants for Fulbright awards, the Committee on International Exchange of Persons conducts two major competitions each year. Between 1 March and 25 April applications are accepted for South America (Argentina, Brazil, Chile, Colombia, Ecuador, Paraguay, and Peru); for South and Southeast Asia (Burma, India, Pakistan, the Philippines, and Thailand); and for Australia and New Zealand. Between 1 June and 1 October applications are accepted for Austria, Belgium, and Luxembourg, Denmark, Finland, France, Germany, Greece, Iceland, Iran, Ireland (outside the Fulbright Act; under a special agreement), Israel, Italy, Japan, the Netherlands, Norway, Spain, Turkey, and the United Kingdom and Colonial Territories. Spain became a participant in the program by an agreement signed in the autumn of 1958, and the first Fulbright grants will probably become available there in 1960–61. Application forms and additional information may be obtained from the Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Avenue, NW, Washington 25, D.C.

The Smith-Mundt program, under which approximately 75 Americans are annually awarded lecturing appointments in countries not included in the Fulbright program, does not operate on the basis of a general competition. Requests for lecturers from participating countries are received very irregularly, and occasionally involve direct invitations. To aid in filling Smith-Mundt lectureships and also certain Fulbright grants not filled through the open competition, the Committee on International Exchange of Persons is developing a Register of Scholars. The register is a biographical reference file of scholars interested in the possibility of overseas assignments. It contains information on their fields of competence, preference as to countries, probable periods of availability, foreign language competence, and related qualifications. Persons with college or university teaching experience are invited to register with the committee and they should request a special form.

Gravity. The Gravity Research Foundation, New Boston, N.H., has announced the 1959 awards for essays on gravity. Five awards, ranging from a $1000 prize to a $100 prize, will be made on 1 June for the best 1500-word essays on the possibilities of discovering: (i) some partial insulator, reflector, or absorber of gravity; (ii) some alloy, or other substance, the atoms of which can be agitated or rearranged by gravity to throw off heat; or (iii) some other reasonable method of harnessing, controlling, or neutralizing gravity. Essays must be received at the foundation's office *before 15 April*. They will be accepted from anyone who is seriously interested in the application of gravity to practical uses for the benefit of humanity.

Teaching. Approximately 9000 secondary-school teachers of science and mathematics will benefit during the academic year 1959–60 from 182 National Science Foundation In-Service Institutes conducted by United States colleges and universities. The In-Service Institute program started with two institutes in the spring of 1957. During the present school year there are 85 institutes offering part-time study to secondary-school teachers.

Institute meetings are held outside regularly scheduled school hours—that is, evenings, Saturdays, or late afternoons—so that teachers may attend while they are still teaching full time in their schools. A typical institute might meet once a week for 2 hours for the full academic year of about 30 weeks. Teachers participating in these institutes will receive financial support in the form of allowances at the rate of 7 cents per mile for travel from their homes to the institutes. Those teachers granted support will not have to pay tuition and fees. Participants will be chosen by the institutes, not by the National Science Foundation.

Scientists in the News

LOGAN WILSON, sociologist and president of the University of Texas, has been nominated by President Eisenhower to replace T. KEITH GLENNAN on the National Science Board. Glennan is head of the new National Aeronautics and Space Administration.

DEREK H. R. BARTON, professor of organic chemistry at the Imperial College of London and a specialist in the chemical structure of natural products, has won the first Roger Adams Award in organic chemistry. The presentation will take place on 16 June during the National Organic Chemistry Symposium of the American Chemical Society's Division of Organic Chemistry in Seattle, Wash.

The biennial award, consisting of $5000 and a gold medal, is sponsored by two chemical publications *Organic Reactions* and *Organic Syntheses,* and administered by the American Chemical Society. The original impression of the medal will be presented to ROGER ADAMS, professor emeritus of the University of Illinois, in whose honor the prize was created.

ROBERT A. W. CARLETON, president and founder of Carleton Company, Inc., has been named the 1959 recipient of the Egleston Medal, Columbia University's highest award for "distinguished engineering achievement."

STANHOPE BAYNE–JONES, former chairman of the Secretary's Consultants on Medical Research and Education, Department of Health, Education and Welfare, is the recipient of the $5000 Passano Award for 1959. The award will be presented at a reception and dinner on 11 June during the convention of the American Medical Association in Atlantic City, N.J.

OTTO HAHN, president of the Max Planck Society, Germany, and winner of the Nobel Prize for the discovery of uranium fission, has received the Grand Cross of the Federal Republic's Order of Merit. President Heuss presented the award on Hahn's 80th birthday at a ceremony in Göttingen. On the same occasion Hahn was also made a member of the French Legion d'Honneur by order of President Charles de Gaulle.

DONALD H. MENZEL, director of solar research at the Harvard University Observatory, has been appointed vice president of the Geophysics Corporation of America and will head the newly formed Astronomics Division.

JOSEPH W. BARKER has retired as chairman of the board of the Research Corporation. He joined the corporation in 1934 as director and was president and chairman of the board from 1946 to 1957. From 1954 to 1957 he was chairman of the board of Research-Cottrell, Inc., a subsidiary in Bound Brook, N.J. He was dean of engineering at Columbia University from 1930 to 1946 and special assistant to the Secretary of the Navy from 1941 to 1945.

The following psychiatrists from abroad visited the University of Pennsylvania School of Medicine's department of psychiatry on 23 March and attended a special round-table conference on psychiatric education: HANS HOFF, chairman of the department of psychiatry, University of Vienna; PIERRE DENIKER, senior lecturer, University of Paris; ROLAND KUHN, professor of psychiatry, University of Zurich; MICHAEL SHEPHERD of the department of psychiatry, University of London; and HANNS HIPPIUS of the department of psychiatry, University of Berlin.

HERBERT BUTTERFIELD, master of Peterhouse and professor of modern history at the University of Cambridge, Cambridge, England, inaugurated the new Horblit lecture on the history of science at Harvard University on 24 March. His subject was "The History of Science and the Study of History."

GROVER LOENING, director of the Flight Safety Foundation, the New York Airways, and the Fairchild Engine and Airplane Company, inaugurated the Lester D. Gardner lectures on the history of aeronautics at Massachusetts Institute of Technology on 10 April. He discussed "Lessons from the History of Flight."

DAVID E. ROGERS, associate professor of medicine and chief of the division of infectious diseases, New York Hospital, Cornell Medical Center, has been appointed professor and head of the department of medicine at Vanderbilt University School of Medicine.

WILLIAM J. LACY, senior chemist in waste-disposal research at Oak Ridge National Laboratory, has been appointed chief radiochemist in research and development by the Office of Civil and Defense Mobilization in Battle Creek, Mich.

ERNEST F. SWIFT, executive director of the National Wildlife Federation, received the Leopold Award, which is given for outstanding service, during the annual banquet of the North American Wildlife Conference in New York City. Other Wildlife Award winners included: FRED J. SCHMEECKLE, Wisconsin State College; HOWARD R. MENDELL, Maine Cooperative Wildlife Research Unit; MILTON B. TRAUTMAN, Columbus, Ohio; RAYMOND J. H. BEVERTON and SIDNEY J. HOLT, United Kingdom Ministry of Agriculture, Fisheries and Food.

The William Pyle Philips lectures at Haverford College will be delivered by two visitors from Cambridge University, Cambridge, England. On 20 April, F. H. C. CRICK of the Institute of Molecular Biology will speak on "Structures and Replication of DNA," and on 27 April VERNON M. INGRAHAM will speak on "Genetic Control of Protein Structure."

Recent Deaths

DAVID H. BARASH, New York; 72; Rumanian-born internist, who had taught at Bellevue and Polyclinic Hospital Medical Schools; 20 Mar.

LEONARD BLUMGART, New York; 78; president of the New York Psychoanalytic Society, 1924–45; taught at New York Psychoanalytic Institute, 1938–50; 20 Mar.

LEOPOLD CASPER, New York; 99; German-born urologist, who invented the uretercystoscope; former professor of urology at the University of Berlin and former chief of urology at St. Francis Hospital in Berlin; author of *Manual of Cystoscopy* and *Manual of Urology;* 16 Mar.

BERNICE L. DODDS, Champaign, Ill.; 56; dean of the College of Education at the University of Illinois since 1953; director of the Division of Education and Applied Psychology at Purdue University, 1948–53; instructor and research assistant at Teachers College, Columbia University, 1937–39; 23 Mar.

HAL DOWNEY, Minneapolis, Minn.; 81; hematologist and emeritus professor of anatomy at the University of Minnesota; had been a staff member there for 42 years; 9 Jan.

MILTON ROSENBLUTH, New York; 68; specialist in the treatment of pneumonia and, since 1947, professor of clinical medicine at New York University Medical School; former director of medical research at Goldwater Memorial Hospital; instructor at Fordham University Medical School, 1916–19; 24 Mar.

GEORGE WILSON, Philadelphia, Pa.; 70; clinical professor of neurology at the University of Pennsylvania Medical School and Woman's Medical College; president of the American Neurological Society in 1948; former consultant to the U.S. Public Health Service; 23 Mar.

Erratum: In the letter "Quantitative Gram reaction" by Roland Fischer [Science 129, 684 (13 March 1959)], the symbol λ was omitted in the expression for wavelength in column 3, line 22. The expression should have read $\lambda_{H_2O} = 595$ mμ.

Erratum: On the cover of the 13 March issue, the authors of the report "Predaceous feeding in two common gooseneck barnacles" are incorrectly listed as G. K. Howard and H. C. Stout. G. K. Howard and H. C. Scott wrote the report. On page 718, column 1, the line "Division of Biological Sciences" in Howard's address should have appeared in Scott's address, not in Howard's.

Erratum: The AAAS International Oceanographic Congress is to be held at the United Nations Building in New York from 31 August to 12 September, not from 1 August to 12 September as stated in the news article that appeared in the 27 March issue.

Book Reviews

. . . In Search of Identity. The Japanese overseas scholar in America and Japan. John W. Bennett, Herbert Passin, and Robert K. McKnight. University of Minnesota Press, Minneapolis, 1958. xii + 369 pp. $7.50.

In Search of Identity has great potential usefulness for advisers and instructors of overseas students from Japan and other oriental countries, and for all who are interested in furthering intercultural understanding through exchange-student programs.

It should be rewarding reading for Japanese students who have been abroad and useful to those who are about to go abroad. Indeed, it should challenge orientals to reexamine defense mechanisms against change—mechanisms born of feelings of inferiority that result from years of colonial status or, as in the case of Japan, from defeat and occupation. A feeling of inferiority is a normal consequence of such experiences, but defense mechanisms scarcely provide a sound foundation for acquisition of status.

Part 1, on the historical background (limited to the purposes of the book and necessarily sketchy), provides good perspective. Part 2 reports experiences and reactions of Japanese students in the United States and on their return to Japan, as revealed through interviews and questionnaires. Part 3 presents an analysis of intercultural experience through more extensive case reports and through typological classification (constrictor, adjustor, idealist, and so on).

Readers may well ask why the appendices were not worked into the context. Appendix A is more than relevant to part 1. Appendix B makes part 3 meaningful, at least to students of the problem. And appendix C should have been a major part of the final chapter, for it spells out the "so what" of the study insofar as American colleges are concerned.

I believe the data presented in *Search for Identity* justify a conclusion that would give significant and useful perspective on a major problem of intercultural understanding.

Out of the assimilation of cultural elements, expectancy of change has become a characteristic of American culture. This is continuously sustained by overabundance, change of styles, and built-in obsolescence. Japan has had one nationality and one basic language for 15 centuries, and there is characteristic resistance to ideological change in Japanese culture, if not to technological change. This is reinforced by persistent overpopulation and scarcity of natural resources. Although Western dress has recently been adopted, the best-dressed woman in Japan today wears a kimono that represents all that is oldest and best in Japanese art.

When these two cultures meet, the question is not "Which is right?" Rather, it is "How did the ideas, the traditions of each develop out of experience and come to have validity?" When the problem is approached thus, appreciation and understanding develop, and perhaps ideas change, without challenge and resultant defense mechanisms. The whole problem of status and identity becomes an issue because people try to think *for* each other instead of *with* each other.

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Surface and Radiological Anatomy. For students and general practitioners. A. B. Appleton and others; 4th edition by W. J. Hamilton and G. Simon. Heffer, Cambridge, England; Williams and Wilkins, Baltimore, Md., ed. 4, 1958. xi + 355 pp. Illus. $9.50.

This is the fourth edition of a textbook originally published in 1938. The text has been extensively revised and rearranged. Many original radiographs have been replaced, and a number of new illustrations have been added.

The introductory chapter contains concise statements on individual variation, landmarks, skin and subcutaneous structures, actions of muscles, physical signs, and x-rays. The remaining sections deal with the various regions of the body. For each area there is a discussion of surface anatomy, contours, landmarks, bones, muscles, movements, radiology, vessels, and nerves.

The text is profusely illustrated. The reproductions of radiographs are excellent. There are very clear photographs illustrating surface contours, with adequate labels. The anatomic illustrations are quite diagrammatic, but this is an advantage, for they are free of unnecessary detail; most of them are in color. There are also many excellent line drawings.

The book should be an invaluable aid to the medical student and practitioner and should be very helpful to physiotherapists and persons in allied fields.

It is unfortunate that the tables of onset of ossification and of skeletal fusion are not based upon current information. The dates given for ossification of *post partum* centers and for epiphyseal fusion are far too late, the range is excessive, and no distinction is made between the sexes. Much modern information is available and should have been included in the revision.

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New Knowledge in Human Values. Abraham H. Maslow, Ed. Harper, New York, 1959. xiv + 268 pp. $4.50.

This interesting book is not, as its title might suggest, primarily a report on recent investigations of human values by the methods of empirical science. It is a collection of papers from a conference with the same title, held at the Massachusetts Institute of Technology in 1957 and sponsored by the Research Society for Creative Altruism. Thus, all the contributors accept to some degree or other the value expressed in the statement by Pitirim Sorokin that "the creative, unselfish work of love for humanity at large is the key to the reconstruction of the world," and that this requires "a moral transformation of man."

The main concern of the contributors is, then, the question of how far science supports this accepted value and of what other supports it may receive from areas other than science.

Some contributors (Pitirim Sorokin, Abraham Maslow, Gordon Allport) believe that empirical studies in psychology and the social sciences give positive scientific support to the value of creative altruism. Others, in seeking the same goal, extend the term *science* to include a formal science of axiology (Robert Hartman) or an ontological science of man's essential nature (Kurt Goldstein, Walter Weisskopf, Erich Fromm, Paul Tillich). Still others seek to ground the accepted value by an emphasis upon some aspect of science, such as the "commitments" involved in a scientific theory (Henry Margenau) or in the activity of scientists (Jacob Bronowski). Finally,

some contributors turn their attention to quite other fields—to the domain of human culture built on a biological basis but not reducible to it (Theodosius Dobzhansky, Dorothy Lee, Ludwig von Bertalanffy), or to the characteristics of the esthetic experience (Gyorgy Kepes), or to the Zen experience and the disciplines of which it is the fruit, Daisetz Suzuki).

The volume concludes with a challenging summary and criticism of the papers of the conference by Walter Weisskopf and the replies to this analysis by a number of the contributors.

The papers which make up *New Knowledge in Human Values* present a wide divergence of views held by persons from a wide range of fields. The papers are short, trenchant, and well written. As Bronowski has discerned, there is a deep, underlying difference of attitude on the part of the contributors concerning how much the quest for a value orientation appropriate to modern man can be aided by empirical science. This is indeed a complex problem which must be worked through. It is a merit of this book to have exhibited the problem and laid before the reader some considerations relevant to the issue.

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An Introduction to Probability Theory and Its Application. vol. 1. William Feller. Wiley, New York; Chapman and Hall, London, ed. 2, 1957. xv + 461 pp. Illus. $10.75.

The first edition of this book was very successful, and this second edition should be even more so. Most books which attempt to develop probability theory rigorously are readable from the mathematician's standpoint but assume too much familiarity with recondite branches of mathematics to attract most physicists, engineers, or others needing probability and statistics as tools. They also tend to present abstract discussions largely devoid of applications.

The present book is rigorous but contains a wealth of illustrative material and examples relative to physics, genetics, contagious disease, card games, traffic and queuing problems, industrial quality control, chain reactions, engineering, and statistics. Most of the chapters include numerous problems, ranging from simple exercises to applications and extensions of the text.

This volume is restricted to discrete sample spaces. This is a severe limitation but one which permits the basic theory to be discussed without appeal to measure theory and allows advanced topics such as random walks and Markov processes to be included. A second volume, to include continuous sample spaces, general theory of random variables and their distributions, limit theorems, diffusion theory, and other topics, was promised in the first edition. It is hoped that it will be forthcoming soon.

The author suggests chapters 1 ("The sample space"), 5 ("Conditional probability. Stochastic independence"), 6 ("The binomial and the Poisson distributions"), and 9 ("Random variables; expectation") as a "beginner's course," with browsing in chapter 2 ("Elements of combinatorial analysis") to help develop technique. Chapter 3 ("Fluctuations in coin tossing and random walks") is entirely new and demonstrates some amazing results totally at variance with results expected on the basis of naive intuition. An example is that the probability of heads (or tails) being "in the lead," for a long series of tosses, for about 97.6 percent of the time is 0.20; for 99.4 percent of the time, 0.10. The fraction of the time "ahead" or "behind" is much closer to zero or 1 than to the "expected" value 0.5. With 10,000 tosses, with probability 0.5, there will be fewer than 68 returns to zero, and of these only half will be changes of lead. One wonders how many reasonable experimental results have been rejected as subject to systematic error or how many erroneous conclusions have been drawn because the experimenter did not know of the arc sine law.

Chapter 11 ("Integral valued variables. Generating functions") may be tackled after chapter 9 in an introductory course and is used in chapters 13 ("Recurrent events") and 12 ("Compound distributions. Branching processes"). Limit theorems and fluctuation theory are discussed in chapters 3, 8, and 10; Markov chains in 15 and 16; random walks in 3 and 14; stochastic processes (including "birth" and "death" processes, waiting lines and servicing problems, the Chapman-Kolmogoroff equations, and other topics) in 17 ("The simplest time-dependent stochastic problems"). Many chapters are on an advanced level; many are independent of the others; all are well written.

Some typographical errors were noted, in which exponents or subscripts were missing—for example, page 164 (1.1) where the exponent is omitted (this should be $-\frac{1}{2}x^2$ rather than $-\frac{1}{2}x$); the equation on page 164 (1.10) where y has not been squared; the equation on page 271 (2.5), where λ_2 has lost its subscript; and the equation on page 83 (6.8), where s in the exponent has also not been squared. (Is it chance that 2 has been left out in each case?)

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Systema Helminthum. vol. 1, parts 1 and 2. *The Digenetic Trematodes of Vertebrates.* Satyu Yamaguti. Interscience, New York, 1958. 1575 pp. Illus. $90.

This monumental work on the systematics of digenetic trematodes is the culmination of Satyu Yamaguti's many years of diligent study of actual specimens, and it is based on his exhaustive review of the pertinent, voluminous literature. On the basis that our knowledge of life-histories of Digenea is inadequate to permit the erection of a system based on natural relationships, the author has based his system on the "whole picture of morphological characteristics." Hence, except for orders, he has not dealt with taxa higher than families. He has presented keys and diagnoses for orders to genera and subgenera. In some families he has introduced tribes which are, for example, substantially equivalent to the sub-subfamilies used by Dubois for the strigeatoids. For each genus the type species is stated, followed usually by a list of species, and accompanied at times by notes on life-histories. The author has erected a few new families, many new subfamilies, some new tribes, and a few new genera.

Keys and diagnoses occupy part 1 (979 pages). Part 2 contains a very useful systematic review of the Digenea of vertebrates and their host relationships (36 pages); an extensive bibliography (216 pages); illustrations (109 plates with 1302 figures) done by the collotype process; and an index (131 pages).

The diagnoses have been especially prepared by the author and are based on first-hand information or on the literature. I believe that they are adequate. The keys are, of course, artificial. I have not tested them on specimens for workability. The figures have been reduced considerably, some of them to the point that a reading glass is required for a careful examination of details. With few exceptions there is a figure to illustrate a species of each genus. If possible, the type species is illustrated.

In the plates one error of mislabeling occurs. Figure 1069, plate 89, shows *Postharmostomum laruei* McIntosh but is labeled *P. noveboracense* McIntosh. I noted a few errors in the text—for example, *Riberoia ondatrae* (Price, 1931) Price, 1942, is assigned to the new genus *Pseudopsilostoma* (page 904) on the assumption that the species is not congeneric with *Riberoia* Travassos 1939, but on page 622 this species is referred to the new genus *Pseudopsilotrema* which is both a *nomen nudum* and a synonym of *Pseudopsilostoma*. I have personally examined Price's type and paratypes, including two series of frontal sections, and can vouch for the presence of the esophageal diverticula which are

characteristic of the genus *Riberoia* Travassos, 1939. Comparison of Price's specimens with the description of *Riberoia ondatrae* by Beaver (1939) convinced me that Price and Beaver were dealing with the same species. *Cercaria thomasi McMullen,* 1938, then becomes a synonym of *Riberoia ondatrae* (Price, 1931) Price, 1942. Whether the genus *Riberoia* is correctly assigned to the family Cathaemasiidae Fuhrmann, 1928, cannot be judged with certainty because of the lack of information on the character of the excretory system of *Riberoia.* The diagnosis of the family Cathaemasiidae states that the excretory system is "Y"-shaped, without numerous branches. However, my recent examination of the excretory system of specimens of *Cathaemasia reticulata* (Wright 1879) shows that both stem and forks of the "Y" have numerous lateral branches.

Yamaguti has followed Dollfus (1939) in the partition of the family Troglotrematidae Braun, 1914. However, I believe that the two subfamilies Renicolinae and Collyriclinae do not belong in this family but should have the full family status that has been accorded them by others. The life-history of *Collyriclum* Kossack, 1911, is not known. This genus has small eggs, indicating that it does not belong with the Troglotrematidae. Its position under the skin of the host is not a character of sufficient importance to justify inclusion of the genus in the Troglotrematidae. Possibly it should be assigned family status in the Plagiorchioidea. The genus *Renicola* Cohn 1904 has a very unusual type of cercaria with a large tail with finfolds and also a peculiar excretory system so unlike that of any other known cercarial type as to suggest that the genus should be assigned to a separate family.

On page 929 *Sellacotyle mustelae* Wallace, 1932, is misnamed *Troglotrema mustelae, family Troglotrematidae.* However, *S. mustelae* appears on page 890 under the new subfamily Sellacotylinae which is properly placed, I believe, in the family Nanophyetidae Dollfus, 1939.

Whether Paragonimidae Dollfus, 1939, should stand as an independent family must await the results of further study. The cercaria of *Paragonimus* is microcercous and very similar to the cercariae of *Nanophyetes* and *Sellacotyle,* family Nanophyetidae. Moreover, the excretory systems of the respective cercariae are similar. It is true that in the adults of *Paragonimus* the excretory bladder is cylindrical, whereas it is saccular in the Nanophyetidae. However, in *Paragonimus* the bladder of the metacercaria is saccular, undergoing modification to cylindrical after the parasite enters the final host.

A number of typographical errors have been noted. These are incidental to bookmaking.

It must be recognized that the placing of any given taxa in a taxonomic system is a matter of judgment, and that the weights assigned to a set of characters may differ with the taxonomist. While there can be no full agreement about certain details of the system set forth by Yamaguti, he has, in my opinion, provided students of digenetic trematodes, both beginners and experts, with a very valuable tool. During the early phases of the identification process the use of this volume, because of its completeness, will obviate an extensive search through a widely scattered literature; but for the identification of species it will still be necessary to consult the original sources. There can be no doubt that this volume will greatly further the study of the Digenea.

The foreword is by E. W. Price, formerly head of helminthological investigations, Animal Disease and Parasite Research Branch, U.S. Agricultural Research Service.

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The Transvaal Ape-Man—Bearing Cave Deposits. Transvaal Museum Memoir No. 11. C. K. Brain. Transvaal Museum, Pretoria, Union of South Africa, 1958. 131 pp.

The discovery of abundant remains of australopithecines ("ape-men") in southern Africa has truly revolutionized many earlier views of human evolution. Hitherto only the first known site of Taung(s) in eastern Bechuanaland has received detailed geological study (by F. E. Peabody). In this publication C. K. Brain presents the first detailed analysis of the situation, mode of origin, stratigraphic structure, and cave-deposit sedimentation of the four other australopithecine sites, all in the Transvaal.

The study is in two main parts. The first section—essentially methodological—presents observations on dolomite caves, their origin by solution or subsidence, and the origin and nature of the cave fillings, both before development of a substantial surface connection (fillings such as stalactites, stalagmites, travertines, residual cave earths) and after development of such a connection (cemented breccias, and so on). The establishment of a condition of equilibrium with the surface permits an assessment of outside conditions through an analysis of the composition of the fossiliferous, cemented, surface-derived soils (breccias). A comparative base line is provided by present-day dolomite soils from regions of differing rainfall in southern Africa. The methods of breccia analysis, all of which have climatic implications, are based on (i) angularity of siliceous sand grains, (ii) percentage of carbonate cement, (iii) quantity of weathered dolomite fragments, (iv) breccia color, (v) grading of sediments, and (vi) ratio of chert to quartz grains.

The second part of the study constitutes a careful application of these methods of analysis to the four sites of Sterkfontein, Swartkrans and Kromdraai (near Krugersdorp) and the Makapan Limeworks (near Potgietersrust), in southern and central Transvaal. The combined result of these investigations indicates that the Sterkfontein accumulations covered an extensive dry phase (30 to 22 inches of rainfall); the Limeworks accumulation covered the end of a long, more intense dry phase; the Swartkrans accumulation covered a brief dry phase followed by somewhat damper conditions; and the Kromdraai accumulation covered a considerably wetter phase (about 40 inches of rainfall). The temporal relation of the sites, listed above in the order of their respective ages, is determined by the associated mammalian faunas. Brain regards the three older sites as all falling within a major dry interpluvial stage (with at least three separate peaks) and the youngest site (Kromdraai) as falling in a succeeding wetter pluvial stage. These climatic phases are tentatively tied to the Kageran/Kamasian interpluvial and the early Kamasian pluvial succession of the late Lower and early Middle Pleistocene. Since this succession is not yet clearly established in eastern Africa, where tectonics and faulting played an important role in creating and draining lakes, I feel that any such correlations must be regarded as provisional.

This meticulous and thorough study is a major contribution not only toward a clearer understanding of the australopithecine sites but also toward a more accurate conception of Pleistocene climates of a part of sub-Saharan Africa. The methods employed should have a broad usefulness both in Pleistocene geological and in prehistoric archeological studies.

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An Introduction to the Theory of Integration. Adriaan C. Zaanen. North-Holland, Amsterdam; Interscience, New York, 1958. ix + 254 pp. $7.25.

Since the publication in 1937 of Saks' now classic *Theory of Integration,* new trends have brought about a great deal of change. The set theoretical approach in measure and integration, already present in Saks' book, has become an essential part of the theory. The linear ap-

proach in functional analysis, introduced by Banach, has permeated most parts of analysis. The present book is an excellent introduction to the subject, with emphasis on the two trends just mentioned. The author, whose large monograph on linear analysis appeared in 1953, has used in the present volume a great deal of balance and restraint. The choice of topics and the structural economy are commendable. Through this book the student may have easy access to more general approaches to measure and integration, such as Bourbaki's or Carathédory's.

At the outset the equivalence of Zermelo's axiom of choice with those of Kuratowsky and Zorn is proved. The concept of measure is introduced as an additive set function in a semiring of sets. Emphasis is given to the extension process generating an exterior measure on a larger class of sets and then a new measure in the subclass of the corresponding measurable sets. The concept of integral is introduced as the Stone version of the Daniell integral. The very same process of extension mentioned above is here used, starting from any linear operator which satisfies a given set of axioms. The Lebesgue-Stieltjes integral is viewed as a particular case of the previous one, and space is given to Fubini's theorem. Normal linear spaces, Banach spaces, and Hilbert spaces are discussed, with emphasis on the fact that bounded linear functionals on a normal space themselves form a Banach space, the conjugate space. The Radon-Nikodym theorem is given for integrals, and the usual version for measures is deduced as a corollary.

Important complements and applications are given: change of variables in Lebesgue integrals; differentiation of integrals in abstract and Euclidean spaces; the Banach-Steinhaus theorem; unitary transformations in Hilbert spaces (in particular, Fourier transformations); and ergodic theory.

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World of Learning, 1958–59. Europa Publications, London, 1958. xiii + 1139 pp. $22.

This useful reference volume gives information on educational, technological, and cultural institutions in more than 100 countries. For each country, information is given about learned societies and research institutions (names, addresses, publications, principal officers, number of members, and sometimes names of members); libraries, museums, and art galleries (names, addresses, size and nature of collections, publications, names of officers, and sometimes a brief historical description); colleges and universities (names, locations, chief officers, enrollment, and sometimes names of professors).

It includes an introductory section on international agencies—UNESCO, the International Council of Scientific Unions, and others—and an index of institutions.

New Books

Advances in Virus Research. vol. VI. Kenneth M. Smith and Max A. Lauffer, Eds. Academic Press, New York, 1959. 390 pp. $10. Contents: "The purification of plant viruses" (R. L. Steere); "Biochemistry of plant virus infection" (C. A. Porter); "The spread of plant viruses" (L. Broadbent and C. Martini); "Physiological aspects of bacteriophage genetics" (S. Brenner); "Purification and properties of poliovirus" (F. L. Schaffer and C. E. Schwerdt); "Measles virus" (F. L. Black, M. Reissig, J. L. Melnick); "Kappa and related particles in *Paramecium*" (T. M. Sonneborn).

Annual Review of Entomology. vol. 4. Edward A. Steinhaus, Ed. Annual Reviews, Palo Alto, Calif., 1959. 467 pp. $7. Contents: "Insect blood cells" (V. B. Wigglesworth); "Culture of insect tissues" (M. F. Day and T. D. C. Grace); "Pheromones (Ectohormones) in insects" (P. Karlson and A. Butenandt); "Insect pigments" (R. I. T. Cromartie); "Taxonomic problems with closely related species" (W. J. Brown); "Ecology of Cerambycidae" (E. G. Linsley); "Biology of Aphids" (J. S. Kennedy and H. L. G. Stroyan); "The biology of parasitic hymenoptera" (R. L. Doutt); "Bioclimatic studies with insects" (P. S. Messenger); "Ethological studies of insect behavior" (G. P. Baerends); "Experimental host-parasite populations" (T. Burnett); "Biological control of weeds with insects" (C. B. Huffaker); "Microbial control of insect pests" (Y. Tanada); "On the mode of action of insecticides" (F. P. W. Winteringham and S. E. Lewis); "Biological assay of insecticide residues" (S. Nagasawa); "Deciduous fruit insects and their control" (M. M. Barnes); "Seed treatment as a method of insect control (W. H. Lange, Jr.); "Fleas and disease" (W. L. Jellison); "Insects and the epidemiology of malaria" (P. F. Russel).

Historian's Handbook. A key to the study and writing of history. Wood Gray *et al.* Houghton Mifflin, Boston, 1959. 58 pp. $1. The purpose of the *Handbook* is to introduce the college freshman and general reader to the nature of history and to offer ideas for effective study, to guide the advanced student when he prepares a term paper or thesis, and to serve as a reference manual.

Our Earth. The properties of our planet, how they were discovered, and how they came into being. Arthur Beiser. Dutton, New York, 1959. 123 pp. $3.25.

Preliminary Archaeological Investigations in the Sierra de Tamaulipas, Mexico. Transactions, vol. 48, pt. 6. Richard S. MacNeish. American Philosophical Soc., Philadelphia 6, 1958. 210 pp. $5.

Progress in Metal Physics. vol. 7. Bruce Chalmers and R. King, Eds. Pergamon, New York and London, 1958. 416 pp. $16. Contents: "Equilibrium, diffusion and imperfections in semi-conductors" (J. N. Hobstetter); "The physical metallurgy of titanium alloys" (R. I. Jaffee); "Thermodynamics and kinetics of martensitic transformations" (L. Kaufman and M. Cohen); "The stored energy of cold work" (A. L. Titchener); "The properties of metals at low temperatures" (H. M. Rosenberg).

Radioisotopes in Scientific Research. Proceedings of the International Conference held in Paris in September 1957 under the auspices of the United Nations Educational, Scientific and Cultural Organization. vol. I, *Research with Radioisotopes in Physics and Industry,* 782 pp., $22.50; vol. II, *Research with Radioisotopes in Chemistry and Geology,* 762 pp., $22.50; vol. III, *Research with Radioisotopes in Human and Animal Biology and Medicine,* 763 pp., $22.50; vol. IV, *Research with Radioisotopes in Plant Biology and Some General Problems.* 791 pp., $22.50 (vols. 1–4, $80 per set). R. C. Extermann, Ed. Pergamon, New York and London, 1958.

Reproduction and Infertility, Third Symposium. Colorado State University, Fort Collins, Colorado. Sponsored by the College of Veterinary Medicine and the Agricultural Experiment Station. F. X. Gassner, Ed. Pergamon, New York and London, 1958. 273 pp. $6.50.

River Basin Surveys Papers. Bull. 169. Inter-Agency Archeological Salvage Program No. 9–14. Frank H. H. Roberts, Jr., Ed. Smithsonian Institution, Washington, D.C., 1958 (order from Supt. of Documents, GPO, Washington 25). 401 pp. $3.25.

Safe Handling of Radio-isotopes. International Atomic Energy Agency, Vienna, Austria, 1958. 99 pp.

Semiconductor Abstracts. vol. IV, 1956 issue. Abstracts of literature on semiconducting and luminescent materials and their applications. Compiled by Battelle Memorial Inst.; sponsored by Electrochemical Soc., Inc. Wiley, New York, 1959. 456 pp. $12.

Statistical Quality Control. An introduction for management. Douglas H. W. Allan. Reinhold, New York; Chapman & Hall, London, 1959. 129 pp. $3.50.

A Taxonomic Study of the North American Licinini with Notes on the Old World Species of the Genus Diplocheila Brulle (*Coleoptera*). Memoirs, No. 16. George E. Ball. American Entomological Soc., Philadelphia, Pa., 1959. 263 pp. $10.

Textbook of Physiology and Biochemistry. George H. Bell, J. Norman Davidson, Harold Scarborough. Williams and Wilkins, Baltimore, ed. 4, 1959. 1066 pp.

Time, Life, and Man. The fossil record. R. A. Stirton. Wiley, New York; Chapman & Hall, London, 1959. 569 pp. $9.

Work Measurement. Virgil H. Rotroff. Reinhold, New York; Chapman & Hall, London, 1959. 203 pp. $4.85.

Reports

Gestation Period and Twinning in Chimpanzees

Abstract. The length of the gestation period in 118 births in a colony of chimpanzees was found to be 226.8 days, with a standard deviation of 13.3 and a range of 196 to 260 days. Six pairs of twins were born in 120 parturitions; thus the apparent twinning rate is higher than that in man.

Yerkes and Elder (*1*) reported that 20 chimpanzee births occurred in these laboratories up to 1 July 1937. Nissen and Yerkes (*2*) described an additional 29 cases, including one twin birth, for the period ending 1 April 1943. Both papers describe certain behavioral and physiological correlates of parturition. The present report (*3*) includes the data in the two previous papers and supplements them with information on births that occurred up to 1 August 1958. Among the 125 offspring obtained in these laboratories, there were 106 live single births, 6 single stillbirths, 6 pairs of twins (one pair of which was stillborn), and 1 case in which the gestation period is unknown. The number of pregnancies terminating in live or stillbirths for the 26 mothers varies from 1 to 11, with a median of 3.5. Miscarriages (defined by less than 190 days' gestation) are not included.

The estimated date of conception was calculated according to the method described by Nissen and Yerkes (*2*), who utilized the beginning of detumescence as a point from which ovulation can be determined. In the 118 parturitions (counting each twin birth only once) for which the duration of gestation period could be calculated, the mean gestation period is 226.8 days, with a standard deviation of 13.3 and a range of 196 to 260 days. Two of the cases fall more than two standard deviations above the mean; these two gestation periods are 258 and 260 days, with the next highest value being 248 days. It is possible that an error in recording one menstrual cycle for each of these animals resulted in the unusually long gestation periods. If these two cases are omitted from the computations, the mean gestation period becomes 226.2 days, with a standard deviation of 11.8 ($N = 116$). The mean gestation period for viable single births only (with twins, stillbirths, and the two doubtful cases omitted) is 227.8 days, with standard deviation of 10.6 and N of 104. No significant differences were found between male and female offspring in duration of gestation period.

Nissen and Yerkes (*2*) found that the variability among the several pregnancies of individual chimpanzee mothers was greater than the variability among the averages for the same animals, in contrast to the findings of Hotelling and Hotelling (*4*) in man and to the statement of Snyder (*5*) in his review of several species. Nissen and Yerkes attributed the discrepancy to the relatively small N on which their computations were based. The number of multiparous females has now been increased to 21 (accounting for 111 births), and the direction and magnitude of the discrepancy persist. The mean average deviation in gestation period for the 21 mothers with plural offspring is 7.8 days, while the average deviation of the means for the same animals is 5.3 days.

The duration of early pregnancies tends to be greater than that of later ones, although there is considerable variability among animals in this respect. The median gestation periods for the first six pregnancies (ten or more cases for each median) are 234, 231, 227, 228, 229.5 and 224 days, respectively.

Statistics for birth weights have not changed significantly from those reported by Gavan (*6*).

The 92 parturitions which occurred in the period from the first colony birth in 1930 until late in 1951 produced one pair of twins; this ratio leads to the conclusion that the rate of twinning in the chimpanzee approximates that of man. Since November, 1951, however, five additional pairs of twins have been born in 28 parturitions, raising the over-all twinning rate to 5 percent of the births. The reasons for the apparent increase in rate of twinning are not clear, but it is interesting to note that Breitinger (*7*) predicted in 1951, "Ich möchte glauben, dass, wenn in der Station [Yerkes Laboratories] künftig mehr und mehr ältere Weibchen mit mehreren vorausgegangenen Geburten zur Zucht gelangen, die Zwillingsgeburten eher zunehmen werden." The six pairs of twins were born to mothers ranging from 15 to 31 years of age at the time of parturition and represented the first, second, third, fourth, fifth, and eighth positions in ordinal of birth for the various mothers. An apparent increase in twinning rate in a colony of captive chimpanzees may be interpreted in light of Fischer's (*8*) theory of twinning as a newly acquired character consequent to man's "domestication" [as opposed to Schultz's (*9*) view that twinning occurs at roughly the same rate in most primates].

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References and Notes

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7 November 1958

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper. (Since this requirement has only recently gone into effect, not all reports that are now being published as yet observe it.)

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* 125, 16 (1957)].

Technique for Differential Reinforcement of Rate of Avoidance Responding

Abstract. A new avoidance conditioning procedure generates high rates of responding compared with previously used procedures. The effect of manipulation of one of the important temporal parameters in the procedure is reported.

In Sidman's initial series of avoidance experiments (*1, 2*), rats were given an electric shock through a grid floor at regular intervals unless a lever was depressed by the animal. Each lever depression reset the timer controlling the

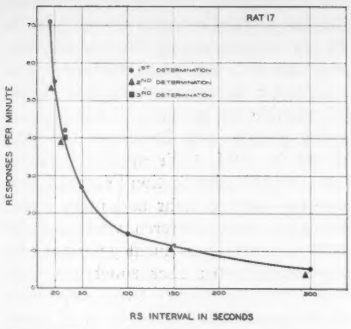

Fig. 1. Rate of avoidance responding as a function of the RS interval.

shock, thus delaying its occurrence. If, for example, each depression of the lever reset a 30-sec timer, a minimum interval of 30 sec was insured between avoidance behavior and shock. Following Sidman's usage, the time interval between a response and shock will be labelled the RS interval and the time interval between successive shocks, when no responding occurs, the SS interval.

The technique permits use of the rate of responding as a continuous and direct indicator of the effects of experimental manipulations. Its usefulness for the study of more complex behavioral phenomena, however, is limited by the fact that at RS > 90 sec the rate of responding drops to a very low level (*2*). In some animals a stable rate of responding cannot be maintained at such low response rates (*3*). At RS = 20 sec no rats were ever observed to emit a sustained rate of more than 20 responses per minute. This is true for any value of the SS interval or the shock level so far employed (*2–4*). The present report demonstrates that a simple modification of Sidman's original procedure can generate extremely high rates of responding. Instead of requiring only a single response on the part of the animal to reset the RS interval, a number of responses had to be made before a new RS interval was started. These responses had to be emitted within the time of the RS interval to avoid shock. The introduction of this additional contingency in the avoidance schedule made the procedure analogous to the "differential reinforcement of high rate" (DRH) schedules described by Ferster and Skinner in the case of positive reinforcement (*5*). In the present case, the lowest reinforced rate was equal to the number requirement divided by the RS interval.

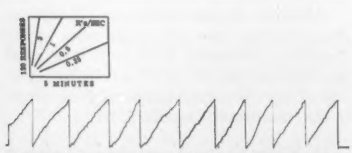

Fig. 2. Portion of the cumulative response record obtained during a session at SS = RS = 30 sec and RR = 8. An oblique pip on the record indicates the occurrence of a shock.

The data reported here were obtained from a single male hooded rat approximately 6 months old at the start of the experiment. The animal was initially conditioned at SS = 3 sec and RS = 30 sec. The shock was provided by a constant-current generator passing half-wave 60-cy current at 1.5 ma. The shock duration was 0.2 sec. The experimental space was 4½ in. wide, 10 in. long, and 7 in. high and was provided with a stainless-steel grid floor. A grid-scrambler, which alternated the polarity of each grid rod, ensured that the animal would receive a pulsating shock regardless of which rod it was standing on. A modified Switchcraft No. 3002 switch was used as a lever (*6*).

After the rate had become reasonably stable, the avoidance schedule was changed to SS = RS = 30 sec and, later, to a requirement of two depressions of the lever to reset the RS timer. During subsequent sessions the animal was gradually shifted to a higher number requirement. Each shock reset the stepper relay which programmed the number of responses required to restart the RS interval. Once the animal gave a stable performance at SS = 30 sec, RS = 30 sec and RR = 8, the RS interval was used as the independent variable of the experiment. The animal was successively run with the following sequence of RS intervals: 30, 300, 30, 150, 100, 50, 30, 20, 15, 150, 20, and 300 sec. Four 6-hr sessions were given at each value. Eight sessions totalling 48 hr were given at the final value of 300 sec. The animal was run every other day.

Figure 1 shows the rate of responding as a function of the RS interval. Each value represents the mean rate of responding during the last 4 hr of the last two successive sessions at each RS value.

As with Sidman's original schedule, where the number requirement was equal to 1, the rate of responding is a logarithmic function of the RS interval (*2*). The present data can best be described by the following equation, which was fitted by the method of least squares

$$y = 157.38 + 0.1588x - 79.84 \log x$$

in which y represents the rate of responding in minutes and x the duration of the RS interval in seconds. A cumulative record of a segment of a daily performance at SS = RS = 30 is shown in Fig. 2. The curve shows that, in spite of the number requirement's being 8, the performance is characterized by a low shock rate when compared with previously obtained data (*2, 4*). It also gives an impression of the stability of the rate of responding during a session. An important feature of the present data is that at RS = 300 sec a substantial rate of 5.6 responses per minute was still maintained. At SS = RS = 30 sec the present schedule generated a rate of 54.9 responses per minute, which is more than twice the highest rate ever observed with the original avoidance schedule. The general features of these data have been confirmed with several other animals with different number requirements.

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15 October 1958

Biochemical Basis of Mating in Yeast

Abstract. One mating type of the yeast *Hansenula wingei* possesses a specific protein on its cell surface which is complementary to a specific polysaccharide on the cell surface of the opposite mating type. The initial phase of mating in which cells of opposite types combine is therefore analogous to a reaction between an antibody and a polysaccharide antigen.

The heterothallic microorganisms probably possess the simplest type of sexual differentiation known. In the haploid stage there are two mating types, identical morphologically and metabolically, but different in genetic composition and in their mating behavior. Mating types in heterothallic organisms are characterized by the fact that cells of one type will mate only with cells of the other type, but not with themselves. In this way they differ from homothallic organisms, in which individuals of the same genetic constitution are able to mate. There are a number of heterothallic species of yeast. These species are especially valuable for studies of the basis of heterothallism, for the haploid cells are the vegetative phase of the organism and are as well the gametes which mate. Two haploid cells of opposite mating type will fuse when they are brought into contact under appropriate conditions, and a diploid cell is formed. No good evidence

has been presented to explain the behavior of mating types on a biochemical basis, although the phenomenon of heterothallism was first discovered in 1904.

Recently Wickerham (*1*) discovered a new species of yeast, *Hansenula wingei,* which is especially suited for studies on the nature of heterothallism. When suspensions of vegetative cells of the two mating types (strains 5 and 21) are brought together under appropriate conditions, a mass agglutination of the cells takes place, indicating a strong attractive force between the two mating types. Once the cells are in intimate contact, cell fusion and diploid formation can promptly proceed. The efficiency of conjugation is probably considerably higher in this yeast than in other species.

Since the agglutination reaction is visible macroscopically, it has been possible to develop an assay for this phenomenon and to study this initial phase of the mating process in a quantitative way (*2*). Previous work has shown that the components responsible for the agglutination are present on isolated cell walls (*3*), indicating the strictly surface location of the mating components.

The mating component of one of the mating types (strain 21) has been shown to be removable by trypsin, and is probably a protein (*3*). The mating component of the other mating type (strain 5) has been shown to be probably *not* a protein, both by its insensitivity to proteolytic enzymes and by its insensitivity to protein extractants such as 80-percent phenol. It was hypothesized that the mating component of strain 5 might be a polysaccharide, so that the agglutination reaction would then be due to a combination between a protein structure in one cell type with a complementary polysaccharide structure in the other cell type. The chemical forces holding the cells together would then be hydrogen bonds, and it has been shown that substances which break hydrogen bonds, such as urea, are able to prevent agglutination or bring about deagglutination (*4*).

It has now been possible to adduce evidence for the necessity of a polysaccharide for agglutination of strain 5, by employing the technique of periodate oxidation first used to demonstrate the carbohydrate nature of the influenza virus receptor of the red blood cell (*5*). Highly agglutinable cells of strains 5 and 21 were treated separately with 0.001*M* sodium periodate for varying periods of time. The cells were then washed and tested for agglutination against untreated cells of the opposite type. Figure 1 (top) shows the results of this experiment. It can be seen that the agglutinability of strain 5 drops rapidly, while that of strain 21 is relatively unaffected.

Since periodate functions by breaking bonds between carbon atoms containing adjacent hydroxyl, or hydroxyl and amino groups (*6*), this means that the mating component of strain 5 probably contains such groups. Hotchkiss (*7*) has tested a large number of biological substances and has shown that polysaccharides are the only common substances sensitive to periodate oxidation which would be present on the yeast surface. Figure 1 (bottom) presents data on trypsin action on strains 5 and 21 and clearly reveals that these two strains show exactly the opposite behavior with trypsin as with periodate. The parts of Fig. 1 together provide good evidence that there are biochemical differences in the cell surfaces of the two mating types.

The hypothesis that mating agglutination is due to configurations of specific macromolecules, polysaccharide and protein, seems to be quite tenable. Such a hypothesis would explain the highly specific nature of the mating agglutination, since diploid hybrids of strains 5 and 21 show no agglutinating characteristics with either haploid strain. Chemical procedures for the extraction of these components have been developed, but as yet it has not been possible to demonstrate the agglutination reaction in extracts, possibly because the amount of material of specific configuration per cell may be very small. The present results reveal for the first time biochemical differences between mating types of a heterothallic organism which seem to explain its mating behavior, and they show that there is a possibility of studying, at the molecular level, one of the results of gene action (*8*).

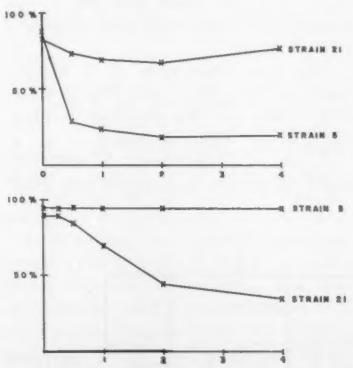

Fig. 1. (Top) Periodate oxidation, 0.001*M* sodium periodate at 37°C for times indicated on the abscissa (hours). (Bottom) Trypsin digestion, 100 μg of trypsin (1:250, Difco) per milliliter in 0.02*M* tris(hydroxymethyl)aminomethane buffer, *p*H 8.0, at 37°C, for times indicated (hours). Agglutinability was tested against untreated cells of opposite type in 1 percent $MgSO_4$, by a quantitative method previously described (*2*). Values are percentage reduction in turbidity of agglutinated over unagglutinated controls; greater reduction in turbidity means stronger agglutination.

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12 November 1958

Bound Phosphorus and Growth of Phytoplankton

Abstract. No correlation was found between phytoplankton pulses in four North Carolina ponds and variations in bound phosphorus. It is concluded that the interaction of a complex of chemical and physical factors produces both seasonal fluctuations and sporadic blooms of phytoplankton.

The problem of the causes for the sometimes sudden and enormous increases in phytoplankton populations, as well as the more regular seasonal variations, has intrigued limnologists and phycologists almost since the discovery of plankton. Pearsall (*1*) suggested that phosphorus is a limiting factor. While some laboratory work such as that of Rodhe (*2*) seems to support this theory, field investigations have shown no correlation between variations in dissolved phosphorus and phytoplankton pulses. In a critical examination of this problem, Hutchinson (*3*) concluded that periodicity in phytoplankton is the result of the interaction of a complex of chemical and physical factors. Recently Abbott (*4*) has suggested that phytoplankton derive their phosphorus directly from complex polyphosphates or organic phosphorus compounds in colloidal matter. He found, however, "an apparent high negative correlation between non-phosphate phosphorus and plankton algae counts."

We have attempted to prove whether there is a correlation between variations in numbers of phytoplankton organisms and variations in total phosphorus in four central North Carolina ponds. We chose two ponds in the lower Piedmont having a high colloidal clay content and two ponds in the upper Coastal Plain only 15 to 20 miles away which have a much lower concentration of colloids in the water. The data ob-

tained consist chiefly of weekly Sedgwick-Rafter counts of phytoplankton and analyses of total phosphorus from water samples taken the same day. A number of estimates of nannoplankton and analyses of soluble phosphorus were also made during the study, which covered three summer months.

While the phytoplankton populations were relatively low, there was considerable variation in numbers from week to week, and several minor blooms were observed. As was expected, total phosphorus also varied considerably, increasing in all ponds after heavy rains.

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5 November 1958

Artificial Neuron

Abstract. An electronic model is described for simulating many of the gross operational functions which are believed to hold for living nerve cells. Synaptic growth is not included. Despite difficulties in drawing very rigorous analogies between the biological cell and its model, a sufficient number of rough similarities exist to make systemic experimentation interesting. Several approaches are mentioned.

Although the complete transmission properties of living nerve cells are not known, many gross behavioral aspects are reasonably well understood. The logical properties of neurons are thought to be generally similar throughout a wide variety of organisms; major differences between different types of cells seem to involve time and level parameters. (A neuron is defined here to include the cell body plus all of its dendritic and axonal appendages.) Using models to simulate the functions of nervous tissue may be useful in understanding or in predicting neurological behavior. Because of the incomplete state of our knowledge of neurophysiology and neuroanatomy, such simulations can be at best only vague and approximate. Nevertheless, these models may be useful as research tools. Several neuron simulations have been previously specified (*1*). This report describes an electronic simulation of a neuron and indicates some of the research which is made possible by such modeling.

To put it in the simplest terms, a neuron may be considered to be an electrochemical black box, essentially a binary-output transducer, having two kinds of input and one output. It is binary only in the sense that, for a given internal state and set of input conditions, it either fires (transmits an output signal) or it does not. It is a transducer in the sense that, independent of the nature of the input signal (it may be electrical or chemical, for instance), a unique standardized electrical output is produced if any output occurs at all. The two types of input are excitatory and inhibitory. Because of complex interacting properties internal to the element, it cannot be considered to be a simple binary switch. It is in fact these very properties which give rise to the complicated behavior we wish ultimately to understand.

The gross properties of a neuron, vastly oversimplified, are described below. These are the functions incorporated in the electronic model.

Input. (i) Inhibition: A particular input connection to a neuron can, while energized, inhibit firing of the neuron by other inputs. (ii) Excitation: Other input connections to a neuron will, if sufficiently energized, always fire the neuron if certain conditions are met. These conditions are described below. (iii) Threshold: A neuron may be fired if the triggering energy supplied to it exceeds a certain threshold value within a time limit. There are input pulses which have insufficient amplitude to cause firing no matter how long they last. This threshold is variable, being a function of the previous history of firing of the neuron. (iv) Refractory period: Immediately after firing, a neuron's threshold rises effectively to infinity and for a period on the order of a few milliseconds, no input signal can fire the neuron again. This absolutely refractory period is followed by a relatively refractory phase. During this second phase a decreasing threshold is observed, approaching the prefiring threshold and reaching it after a few tens of milliseconds. (v) Summation: Two or more input pulses, each of insufficient energy to excite a neuron, can be integrated by the cell so that firing occurs. To be successful, this summation must occur within a maximum time, typically on the order of a millisecond or so. Since these inputs may arrive via different pathways, there can be both spatial and temporal summation.

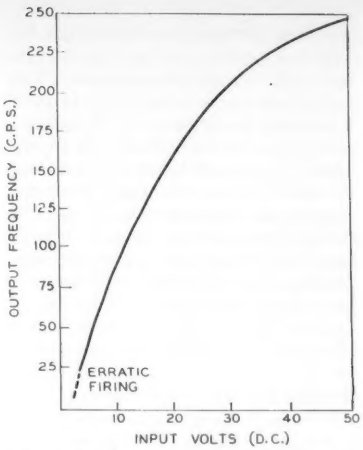

Fig. 2. Typical output firing frequency as a function of input excitatory voltage.

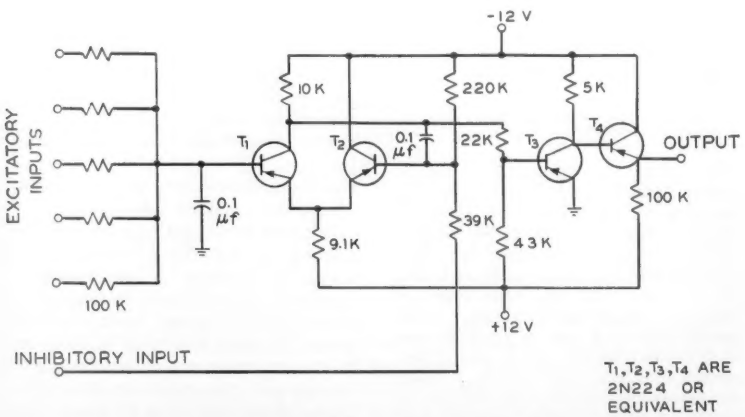

Fig. 1. Transistorized version of artificial neuron having excitation (threshold, summation, refractory) functions, inhibition, and all-or-none output, as described in text.

Output. The output of a neuron is "all-or-none." If firing occurs, then a pulse of standard amplitude and duration is produced. There are exceptions, but as a first approximation we may consider the energy per output pulse to be constant.

A model which realizes these functions can be easily made with electronic circuits. One version is shown in Fig. 1 (*2*). This four-transistor device exhibits the properties of excitation, inhibition,

summation, variable threshold, and all-or-none output, as described.

The model has an integrating time constant of 2 msec and a refractory time constant of about 10 msec, approximating corresponding values in the biological neuron. Quiescent threshold is from 1 to 5 volts (depending on the number of inputs connected), while the output pulse level is 10 volts. These levels are many times greater than those found in nerve tissue (there thresholds are typically 5 to 10 mv; output spike potentials are approximately 50 mv), but the *ratios* between threshold and output levels are commensurate. These ratios in part determine input summation characteristics when several cell outputs combine. The output pulse duration is approximately 4 msec; this is considerably greater than the action spike length found in biological nerve, but it can be shortened at will by use of a suitable differentiating network. The output characteristics are compatible with the input (excitatory and inhibitory) requirements such that a chain or network can be readily assembled. One unit will drive up to 100 others without serious deterioration of output wave form or output level.

This circuit can be used to give either single pulse outputs or variable frequency pulse trains, depending on the nature of the input. A typical direct-current input versus frequency output characteristic is shown in Fig. 2. This mode of operation is useful for simulating peripheral receptors, such as retinal elements, when used in conjunction with suitable transducers.

Photoresistive cells (for example, cadmium selenide) and these neuron models have been used to simulate some of the simple structures and functions of the retina. "On," "off," and "during" receptors are easily produced, as are flicker-fusion phenomena. Mutual inhibition of cells in an array, resulting in spatial differentiating of optical images, is also readily arranged. Similar experiments in audition are contemplated.

The relative simplicity and low unit cost (less than $10) of this model makes feasible network experiments in which large numbers of cells are used. Simple circuit changes to obtain other input and refractory time constants or excitation and inhibition thresholds can be easily made if desired.

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20 October 1958

Isotope Dilution Method for Assay of Inagglutinable Erythrocytes

Abstract. The number of cells that remain free in the presence of agglutinin is usually much larger than the number of inagglutinable cells. The true inagglutinable proportion can be found by successive agglutinations of a labeled population in the presence of unlabeled carrier cells. By this means it is shown that group A persons possess non-A erythrocytes in proportions of the order of 10^{-8}.

Estimation of small proportions of inagglutinable cells has hitherto presented insurmountable difficulties. Ashby (*1*) found a range of 0.03 to 3.5 percent of free cells in human anti-A or anti-B agglutinations. It was uncertain whether the cells remained free because they were truly inagglutinable or because of some other limitation of the reaction. McKerns and Denstedt (*2*) reasoned that if free cells were inagglutinable they would accumulate with successive additions of fresh cells to the reaction mixture. Since successive additions did not increase the free-cell count, the free cells are mainly agglutinable. In these circumstances the count does not reveal the proportion of inagglutinable cells or even if any such cells are present.

If cells are radioactive, they can be distinguished from unlabeled cells added later. Thus initial cells can be traced through many agglutinations with unlabeled "carrier" cells. This eventually removes the labeled agglutinable cells, and the remaining activity represents inagglutinable cells.

An experiment with known mixtures of agglutinable and inagglutinable cells labeled in vitro with sodium Cr^{51}-chromate (*3*) illustrates the feasibility of the method. About 0.03 ml of labeled O cells and 2 ml of unlabeled AB cells were mixed with 25 ml of saline and 10 ml of lima bean extract (*4*) having an anti-A titer of 1:128. A 1-ml sample was removed for Cr^{51} counting. The remainder was agglutinated at 4°C in a 7- by 9-in. pan. The mixture was transferred to a separatory funnel and allowed to settle 5 minutes, and the agglutinated mass separated from the supernatant. One milliliter of supernatant was removed for counting. The remaining volume was noted and returned to a pan with 3 ml of added agglutinin and 3 ml of 66 percent suspension of unlabeled AB carrier cells. This was repeated six times, then 0.5 ml of labeled AB cells was added with the usual carrier and agglutinin. This reaction mixture was sampled for counting, and the experiment continued through five more stages. The supernatant sample at each stage was immediately centrifuged, and the pellet was washed once with saline and counted in a well-type scintillation counter while it was in the centrifuge tube. Preliminary dilutions of reaction mixture and supernatant samples of stage 7 were required to bring them within counting range. In Fig. 1, corrected sample activity is plotted against stage. The inagglutinable cells remain in the system while agglutinable cells added midway in the experiment are swept out.

The dilution owing to additions of agglutinin and carrier was noted at each stage, and the activity was corrected by the cumulative product of prior individual dilution factors. An individual dilution factor does not include the packed-cell volume of carrier which is, in effect, both added and removed between samplings. One might suppose the proper factor to be the ratio of reaction mixture volumes after and before the fluid additions. Reconstruction experiments corrected in this manner, however, showed a paradoxical increase of inagglutinable cells. If the data for Fig. 1 had been so treated, for example, the proportion of labeled cells would have seemed to double within eight stages. Evidently agglutination does not entrap inagglutinable cells but excludes them locally, thus tending to concentrate such cells in the supernatant. We infer that agglutinated cells possess an extracellular volume inaccessible to free cells. Under our experimental conditions this associated volume was about one-third the total volume of the agglutinated mass, since omission of *all* the 66 percent carrier from the calculations for Fig. 1, rather than just its packed-cell volume, nearly compensated for the concentration effect. This unexpected exclu-

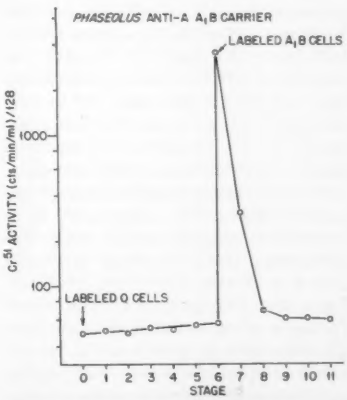

Fig. 1. Reconstruction experiment with inagglutinable O cells and agglutinable AB cells. The point on the left is the initial reaction mixture in which only the O cells are labeled. The following six points are supernatants of successive agglutinations with unlabeled AB carrier cells. The high point is the reaction mixture of stage 7 after the addition of labeled AB cells. The remaining five points are supernatants as before.

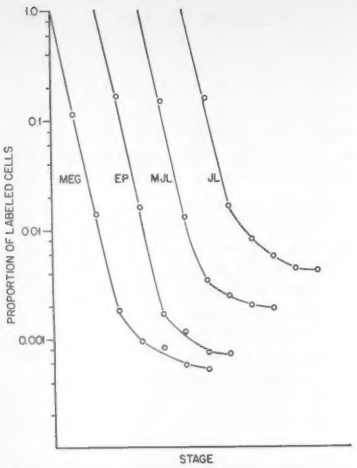

Fig. 2. Determination of the proportion of inagglutinable cells in four normal donors, with respect to lima bean anti-A lectin. The corrected proportion of labeled cells in the supernatant is plotted against the stage. M.E.G. belongs to group A_1B; the others to A_1. The phenotypes of the remaining labeled cells are accordingly B or O (*5*).

sion of free cells is in contrast to the entrapment seen when mixtures are centrifuged (*5*). Clearly, the dilution series is a likely source of error unless it is checked in reconstruction experiments.

To determine the proportion of naturally occurring inagglutinable cells with respect to a given agglutinin, 5 ml of washed cells were labeled and then washed six to eight times in 40-ml aliquots of saline to remove unbound chromate. Labeled cells release small amounts of Cr^{51}, partly by invisible hemolysis and partly by elution with a half-time of 75 days (*6*). Washing was considered sufficient when the supernatant activity was less than 10^{-4} that of an equal volume of cells. The initial reaction mixture (brought to a volume of about 40 ml) contained sufficient agglutinin to give massive agglutination within a few minutes. The components were mixed and sampled quickly before agglutination. The first sample usually required a dilution of 1:1000 for counting, a step facilitated by lysis in water. Inclusion of suspending fluid in the sample introduces no error early in the experiment since the activity in solution at this time is negligible compared with that in cells. Subsequent stages followed the protocol described for the reconstruction experiment (except, of course, that no further labeled cells were added). The total volume decreased 1 to 3 ml per stage but rarely became a limiting factor. Hemolysis during the experiment did not significantly decrease the number of labeled cells but often released enough activity during the first stage to exceed that of the few labeled cells remaining in the last stages. From the third stage on, therefore, the cells must be separated from suspending fluid before samples are counted. Chromium released from cells does not contaminate the carrier. Sedimentable activity other than that in erythrocytes was checked by lysis of pellets with 1 percent acetic acid. As in fresh cells, 80 percent or more of the label was released regardless of the stage tested, indicating that all the sedimentable label is equivalent to erythrocytes.

Progress of the experiment may be visualized in a semilogarithmic plot of stage versus ratio of the corrected activity to initial activity. Figure 2 shows experiments on three AB and one A blood with lima bean anti-A lectin. During the first two or three stages, the proportion of labeled cells removed per stage is remarkably constant; then it decreases as the inagglutinable fraction is approached. After the cells that react with a given antibody have been exhausted, the addition of an antibody of different specificity may result in a further removal of cells (*7*).

Activities of the initial reaction mixtures were in the neighborhood of 2×10^6 count/min ml. These were achieved with Abbot Rachromate containing about 0.03 mg of Cr per milliliter (specific activity about 30 mc/mg of Cr), mixed in 1:5 ratio to cell volume in concentrated saline suspensions and held at room temperature for about 30 minutes. Chromium uptake was less than one-tenth that necessary to increase the mechanical fragility of the erythrocytes (*6*). The inagglutinable cell levels indicated (0.0005 to 0.004) far exceed levels to which the method may be adapted with confidence. With maximum uptake, larger amounts of blood, higher specific activity of Cr, last-stage sampling of all cells, and counter operation at near-background levels, measurement of inagglutinable cells in the proportion of 10^{-6} should be entirely feasible.

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Carbon Monoxide in Green Plants

Abstract. Green plants grown in a closed, illuminated system liberate small quantities of carbon monoxide. Similarly, finely divided powder and chlorophyll extracts of green plants, when illuminated in an environment of oxygen and water, will yield small quantities of carbon monoxide as well as certain aldehydes. The component of the light spectrum which is absorbed in photosynthesis (480 to 680 mμ) was found to be responsible for the CO and aldehyde phenomena.

The literature contains numerous reports concerning the effects of carbon monoxide on the growth and development of plants subjected to varying concentrations of this gas. It is generally agreed that CO in very high concentrations inhibits growth and development, whereas with respect to low concentrations of this gas, the reports are somewhat controversial.

Concerning the natural occurrence of carbon monoxide in green plants, very little work has been reported. In a short report Langdon (*1*) observed CO in the floater of Pacific Coast kelp, *Heterocystis lulkeanea,* and considered it a by-product of respiration. He states that no gas was formed when the plant was killed, and that none was formed when the plant was macerated and allowed to undergo autolysis or decomposition. Rigg (*2*) repeated Langdon's observation on the bladder of sea kelp and also interpreted the CO as a by-product of respiration. Metz and Sjöstrand (*3*) and Sjöstrand (*4*) have reported the endogenous formation of CO in mammals and have attributed the presence of the gas to the oxidation of some methane group in the hemoglobin molecule by the addition of ascorbic acid, with formation of choleglobin and release of CO.

This report concerns the observation and measurement of carbon monoxide in a number of green plants and the possible significance of its presence. The investigation stemmed from observation of unusually high carbon monoxide content in a specimen of human muscle tissue into which a considerable quantity of green vegetation had been impacted during an aircraft accident.

A method for CO determination by means of carbon monoxide sensitive indicator tubes has been developed (*5, 6*) which can be used to determine CO concentrations as low as 2.5 ppm. This sensitivity was also obtained with the Liston-Becker model 15-A infrared CO analyzer. The method is based on the homogenization of a few grams of tissue in a gastight, nitrogen-filled homogenizer in the presence of 30 percent potassium ferricyanide [$K_3F_e(CN)_6$], sodium acetate (*p*H 6), and caprylic alcohol. This is a standard procedure for releasing carbon monoxide from blood. Aliquots of the gas from the homogenizer were removed

and analyzed for CO with the Liston-Becker infrared CO analyzer and with CO sensitive indicator tubes (*6*) in accordance with methods now employed by the U.S. National Bureau of Standards. The CO is expressed as milliliters of CO per 100 grams of tissue at standard temperature and pressure, dry.

Various structural portions of fresh green vegetation — including shrubs, grasses, weeds, evergreen and deciduous trees, and algae—were used in this investigation. The samples included leaves, stems, fruits, and roots. The investigation was subsequently extended to a study of dried green leaves, extracts of dried green leaves, and green plants growing in a closed system. A series of color filters was used to determine the spectral components essential to the liberation of CO by the plant systems.

The results of the analyses of a number of fresh plant structures for carbon monoxide are presented in Table 1. These plant components, obtained between the hours of 10 A.M. and 2 P.M., reveal different CO levels—from a high of 2.1 ml/100 g in alfalfa to none in bleached celery leaves. There was no significant difference in the CO content of alfalfa leaves collected at various times during a 24-hour period. Further evidence of liberation of carbon monoxide from green plants was obtained by shaking 3 kg of chopped, fresh alfalfa leaves with the ferricyanide acetate buffer caprylic alcohol in a large glass jar filled with air for a period of 30 minutes. The gas was drawn off, and the vessel was refilled with air and shaken again. The process was repeated until 6 lit. of gas was obtained. This gas was subsequently scrubbed with bromine water, potassium hydroxide, and, finally, sulfuric acid, before analysis for CO. The percentages of CO concentration, as determined by the indicator tube method, the Liston-Becker infrared analyzer, and the phosphorus pentoxide method (*7*), were 0.344 ± 0.0030, 0.344 ± 0.0025, and 0.345 ± 0.0030, respectively.

Table 1. Carbon monoxide content of plant structures. Values are averages for ten samples obtained near midday.

Plant	CO (mg/100 g of tissue)
Leaves	
Alfalfa	2.100 ± 0.23
Cotton	0.248 ± 0.039
Sage plant	0.745 ± 0.063
Pigweed	0.212 ± 0.023
Morning-glory	0.176 ± 0.014
Cedar	0.368 ± 0.017
Ligustrum	0.487 ± 0.029
St. Augustine grass	0.048 ± 0.017
Combs grass	0.515 ± 0.093
Lettuce	0.001
Celery	No trace
Stems	
Pigweed	0.022 ± 0.002
Alfalfa	0.398 ± 0.05
Spirogyra	0.049 ± 0.008
Carrot	No trace
Pecan husk (green)	0.003

Three mice were exposed to this gas for 20 minutes. They showed a blood CO level of 71.0 ± 2.1 percent, whereas control mice in air showed blood CO levels of 0.20 ± 0.02 percent.

With the "flour" obtained from milling oven-dried (130°F) alfalfa leaves, the following observations were made. (i) Relatively low concentrations of CO were released when the dry flour was placed in an oxygen-filled flask and exposed to sunlight. (ii) Larger quantities of CO (1 ml/g) were released when the illuminated flask contained water in addition to the oxygen and plant flour. (iii) No CO was produced when oxygen was replaced by some inert gas such as helium or nitrogen. (iv) No CO was produced in flasks containing leaf flour, oxygen, and water if the flasks were kept in the dark. (v) Aldehydes were produced, along with CO, in the illuminated flasks containing leaf flour, oxygen, and water. (vi) The carbon monoxide phenomenon was not inhibited by a number of enzyme inhibitors, including cyanides, fluorides, acids, and alkalis. (vii) The effective spectral component for the CO and aldehyde formation lies primarily between 480 and 680 mμ.

Flasks containing hydrated leaf flour and rendered bacteriologically sterile by autoclaving gave results comparable to those obtained with nonsterile systems. This may be observed in Table 2. It is evident that the CO is liberated from those flasks which contain oxygen and are illuminated. Numerous experiments have shown that oxygen is consumed by the hydrated flour in darkness as well as in light but that the CO and aldehydes occur only when the system is illuminated.

Experiments with pigments extracted from leaf flour with various organic solvents gave results similar to those obtained with the leaf flour. The greater CO yield was obtained from the chlorophyll fractions. These pigments were separated from the organic solvents by vacuum distillation, placed in flasks containing oxygen and water, and subsequently illuminated by direct sunlight. The flour remaining after pigment extraction failed to yield CO when it was exposed to light.

R. D. Gafford (*8*), using a closed, illuminated system containing an algae, *Anacystis nidulans*, has shown that CO is evolved from the system during illumination and has obtained CO concentrations as high as 800 ppm during a period of a few days. The accumulated CO appears as a linear function of time, under constant illumination and in the presence of O_2. I made similar observations when large, thin polyethylene-lined cellophane bags were tied securely around branches of trees in such a manner as to make a transparent, gastight environment for the leaves. These bags were filled with various mixtures of O_2, N_2, and CO_2, and samples were removed for analysis under conditions of illumination and darkness. Analysis of the gas at timed intervals revealed accumulation of CO *only* in the illuminated bags containing oxygen. Over a 3- to 4-day period the CO concentration rose to a value of 800 to 900 ppm.

Table 2. Carbon monoxide, O_2, and CO_2 content of gas after 24 hours of illumination. Values are averages of five determinations.

Initial mixture	CO (ml/100 g)	CO (%)	CO_2 (%)	O_2 (%)
100% O_2	70.80	0.30	1.92	−6.80
81.64% O_2; N_2	69.90	0.29	1.60	−7.24
61.68% O_2; N_2	47.60	0.201	1.86	−6.63
39.07% O_2; N_2	46.60	0.195	1.60	−6.67
20.18% O_2; N_2	29.51	0.127	1.59	−4.78
10.35% O_2; N_2	17.92	0.075	1.09	−3.56
4.99% O_2; N_2	11.86	0.052	0.92	−3.43
3.4% O_2; N_2	7.270	0.034	0.45	−2.36
1% O_2; N_2	6.200	0.025	0.36	−0.85
100% N_2	0.247	0.001	0.08	0.12
100% O_2 (light-shielded flask)	2.470	0.010	0.00	−2.82
100% O_2 (chlorophyll extract)	14.180	0.130	1.00	−2.28
100% O_2 (dechlorophyllated)	14.17	0.135	1.76	−6.56

In a final series of experiments, seedlings of *Avena sativa* were dark-grown, and the leaves were harvested and dried in an electric oven. The flour from these plants did not yield CO or aldehydes when it was placed in flasks containing water and oxygen and illuminated in direct sunlight.

The fact that carbon monoxide is observed in injured plants does not necessarily mean that it is present in the normal plant. The experiments, however, seem to point to the natural occurrence of a CO "generator" or precursor substance in green plants, the generation and liberation being brought about through some photodegredative activity involving the chlorophyll system. It appears to occur both in vivo and in vitro and requires light and oxygen.

From the practical side, it would seem that there is a possibility of CO asphyxiation in the proper environment of green, damaged vegetation. In any proposed human-algae closed system, provisions may have to be made to eliminate the CO gas evolved from the plant systems. Even though I have made no measurements by way of verification,

it would seem reasonable to postulate the occurrence of higher blood CO levels in herbivorous animals consuming sizable quantities of green vegetation than in nonvegetarian animals.

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Nemin: a Morphogenic Substance Causing Trap Formation by Predaceous Fungi

Abstract. Broths in which the nematode *Neoaplectana glaseri* had developed axenically caused the mycelium of the predaceous fungus *Arthrobotrys conoides* to differentiate into traps. The active principle was extracted from worm-free culture filtrates and named "nemin." The identity of nemin remains to be established.

Recent reviews by Duddington (*1*) summarized our present knowledge of predaceous fungi. These remarkable microorganisms can capture and kill nematodes by means of traps formed in response to the presence of their prey. The fact that they do not form traps when grown in pure culture, but do so in the presence of nematodes, suggests that some morphogenic substance produced by the worms is responsible for differentiation of the fungus mycelium into traps. Evidence substantiating this was obtained by Comandon and De Fonbrune (*2*) and by Lawton (*3*), who demonstrated that water in which nematodes had been suspended induced trap formation. The list of nematode-free preparations capable of causing predaceous fungi to form traps has been extended to include various animal sera and tissue extracts (*4*). The active principle in water in which nematodes had been suspended was destroyed by boiling (*2*), whereas that in guinea pig serum was thermostable and not affected by alcohol (*5*). The nature of the substance or substances causing trap formation has not been determined.

Table 1. The ability of culture filtrates of *N. glaseri* to cause trap formation by the predaceous fungus *A. conoides*.

Filtrate dilution	Trap formation	
	Uninoculated medium	Inoculated medium
0	–	++
1/5	–	++++
1/10	–	++
1/50	–	+
1/100	–	+
1/200	–	–
1/400	–	–

The nematode *Neoaplectana glaseri* and the predaceous fungus *Arthrobotrys conoides* (*6*) were employed in the present investigations. *Neoaplectana glaseri* was cultivated axenically in meat infusion broth supplemented with raw liver extract. The composition of the medium and the method of culturing the nematode were described by Stoll (*7*). Nematode populations were measured by direct microscopic counts of appropriate dilutions of the broths. Worm-free preparations were obtained by double filtration of broth samples through sterilized filter paper (H. Reeve Angel No. 802) under aseptic conditions. The activity of filtrates was determined by a simple dilution assay. Aliquots of the culture filtrates were diluted quantitatively in a series of sterilized water blanks, and 1 ml of each dilution was added to the surface of petri dishes containing 20 ml of maize-meal agar on which *Arthrobotrys conoides* had developed for 4 days at 28°C. The plates were returned to the incubator and examined microscopically (×100) for trap formation 24 and 48 hours after treatment. The extent to which various dilutions of the culture filtrates caused trap formation by the fungus was recorded. Activity is reported as dilution units, the reciprocal of the highest dilution of a culture filtrate that caused the fungus to form traps.

When a washed suspension of living nematodes was added to the surface of petri dishes on which *A. conoides* had developed, the mycelium differentiated, producing networks of hyphal loops in which numerous worms were captured and destroyed. No traps were formed on plates which did not receive nematodes.

The activity of a broth freed of nematodes and assayed by the procedures described is shown in Table 1. The culture was 9 months old when it was tested. It had been inoculated with approximately 100 worms and supported a population of 110×10^3 nematodes after 6 weeks' incubation. The culture filtrate caused *A. conoides* to form traps and contained at least 100 but less than 200 dilution units of activity. Since uninoculated broth was inactive, the results provided unequivocal evidence that a metabolic product of the nematode was responsible for the formation of traps by the fungus. "Nemin" is proposed as the name of the substance or substances that cause trap formation by predaceous fungi. The morphogenic effect of nemin is illustrated in Fig. 1. The nemin activity of a second 9-month-old culture of *Neoaplectana glaseri,* which had supported 28×10^3 worms after 6 weeks', and 2×10^3 worms after 7-months', incubation, was more than 10 but less than 50 dilution units. The numbers of traps on plates treated with undiluted culture filtrates were consistently less than those on plates treated with low dilutions (1/5, 1/10) of the active broths (Table 1). This suggests that there was a nemin concentration optimal for inducing trap formation, or that the culture filtrates contained a nemin inhibitor which was removed by dilution.

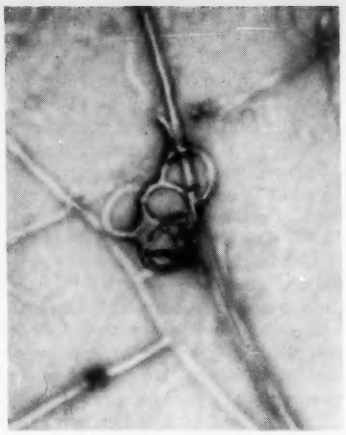

Fig. 1. Nematode-trapping hyphal loops produced by the predaceous fungus *A. conoides* in response to worm-free culture filtrates of the nematode *N. glasseri* (×220).

To determine the time and stage of development at which nemin was elaborated by *N. glaseri,* a 100-worm inoculum was added to each of a series of tubes containing culture medium and the tubes were incubated at 22°C. Individual tubes were withdrawn after 4, 8, 12, 16, 21, 25, and 60 days of incubation. A portion of the contents of each tube was used to determine the number of worms present. The remaining broth was freed of nematodes by filtration and assayed for nemin activity. Following inoculation with third-stage larvae, young *N. glaseri* from the resulting adults first appeared on the fourth day, and the worm population then increased to a maximum in 15 days. The viable count decreased slightly after 21 days of incubation and then tended to remain con-

stant. The 60-day-old culture filtrate induced *Arthrobotrys conoides* to form traps. Broths of younger cultures were inactive, indicating that nemin was not produced during rapid growth and multiplication of the nematode but appeared in the medium after the nematode population had attained a maximum level and when death and disintegration of the worms had commenced.

Nemin is soluble in water, ethyl acetate, and *n*-butanol but not in benzene, carbon disulfide, or ethyl ether. It was not precipitated when culture filtrates were diluted to 5 times their original volume with acetone and was not inactivated by exposure to a temperature of 100°C for 10 minutes. The following procedure for the extraction and concentration of nemin was applied to an equal volume of human blood serum and the filtrate of a broth culture in which *Neoaplectana glaseri* had developed for 4 months: the fluids were diluted with four volumes of acetone and the precipitate formed was concentrated by centrifugation and discarded. The supernatant liquid was dried at room temperature under a hood, and the residue was dissolved in distilled water. The water was twice extracted with an equal volume of *n*-butanol, and the butanol extract was collected by means of a separating funnel and dried at room temperature. The residue was dissoved in distilled water and assayed for nemin activity. Both extracts induced trap formation, indicating that the active principle in serum and in a culture filtrate of *N. glaseri* was similar if not identical. Since the extraction procedure would have eliminated all protein and polysaccharides of high molecular weight, it is doubtful that nemin is related to antigenic materials excreted by some nematodes (*8*). The nature of nemin remains to be determined (*9*).

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Role of Myocardial Catecholamines in Cardiac Contractility

Abstract. In cats bilateral sympathectomy or administration of reserpine results in a marked reduction in concentration of myocardial catecholamines. The contractility of papillary muscles from such animals is significantly less than that of muscles from untreated animals. These findings demonstrate the importance of normal levels of myocardial catecholamines in the maintenance of normal cardiac contractility.

The capacity of reserpine to release norepinephrine and epinephrine from their storage sites provides another approach to the study of the role and mechanism of action of these neurohormones. Our recent experiments (*1*) showed that pretreatment of cats with reserpine, by depletion of the stores of catecholamines, abolished the positive inotropic responses of atropinized papillary muscles from these animals to tetramethylammonium, nicotine, and certain other ganglionic stimulants. Histological examination of the muscles has failed to reveal the presence of any ganglion cells (*2*). These observations indicate that the "nonganglionic" cardiac stimulant activity of tetramethylammonium and nicotine is dependent on the presence and release of catecholamines in the myocardium. Other workers (*3*) have also suggested that the augmented contractility of the myocardium which results from various procedures is due to intracardiac liberation of catecholamines. There is also experimental evidence which indicates that the heart rate of animals whose myocardial catecholamines have been depleted by pretreatment with reserpine is significantly slower than that of normal animals (*4*).

The present studies (*5*) were undertaken in order to determine the relationship of myocardial catecholamines to cardiac contractility. Papillary muscles of approximately equal length and thickness were prepared from cats according to the procedure described by Cattell and Gold (*6*). The muscles were subjected to a resting load of 2.0 g and were stimulated to contract by means of a square-wave stimulator which provided, at supramaximal voltage, 1 impulse per second with a duration of 1 msec. Their isotonic contractile amplitudes were recorded on a smoked drum by means of a lever providing tenfold magnification. After the contraction of the muscles had stabilized, the magnitude of contractile amplitude was measured. The myocardial content of catecholamines was determined spectrophotofluorometrically (*7*), and depletion of catecholamines was accomplished either by pretreatment with reserpine (*8*) or bilateral sympathectomy.

The mean values obtained for the contractile amplitude of papillary muscles and myocardial catecholamines from ten normal cats were 18.0 mm and 1.61 μg/g, respectively (Table 1). The intravenous injection of reserpine caused a marked depletion of myocardial catecholamines within 18 to 20 hours. The mean value in ten animals was approximately 90 percent below that found in untreated cats. The contractility of the papillary muscles from these cats was very weak compared with that of muscles from normal animals; the difference between the two groups was highly significant. It was also found that the papillary muscles from reserpine-treated cats were more readily fatigued than those from normal cats and at the same time were more sensitive to the inotropic effect of epinephrine or norepinephrine.

The afore-mentioned findings could be interpreted as being the result of a direct action of reserpine on the papillary muscle rather than a reduction in the concentration of myocardial catecholamines. To clarify this point similar experiments were performed on papillary muscles of cats whose myocardial catecholamines had been reduced in concentration by bilateral sympathectomy. Under pentobarbital anesthesia, bilateral removal of the stellate and first seven thoracic sympathetic ganglia was accomplished. Between removal of the ganglia on the two sides an interval of 7 to 10 days elapsed. Within 15 to 26 days after the last operation the myocardial catecholamines were found to be decreased by approximately 80 percent. The contractile amplitude of papillary muscles from these animals was depressed to about the same extent as that of muscles from reserpine-treated animals. It is to be noted that administration of reserpine resulted in a significantly greater reduction in cardiac catecholamines ($p < .001$) than did sympathectomy. Yet reduction in contractility was of approximately the same order of magnitude.

It can be concluded that depletion of myocardial catecholamines results in de-

Table 1. Myocardial catecholamine concentrations and contractile amplitudes of papillary muscles from normal, reserpine-treated, and bilaterally sympathectomized cats.

Treatment	Animals (No.)	Myocardial catecholamines (μg/g)*	Contractile amplitude (mm)*
None	10	1.61 ± 0.06	18.0 ± 1.10
Reserpine†	10	0.15 ± 0.03‡	9.7 ± 0.68‡
Bilateral sympathectomy§	9	0.28 ± 0.02‡	10.6 ± 1.05‡

* Mean ± standard error.
† Measured 18 to 20 hours after intravenous injection of 0.05 to 5.0 mg/kg of reserpine.
‡ These values are significantly different from control values ($p < .001$).
§ Measured 15 to 26 days after bilateral sympathectomy.

pression of cardiac contractility. It appears plausible also to conclude that the stores of norepinephrine or epinephrine in the myocardium are important in maintaining normal contractility. It is suggested that the myocardial catecholamines may be released in small quantities under normal conditions to affect the rate of the pacemaker and contractility and serve as humoral agents for the regulation of normal cardiac function.

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Interference with Feedback Control: a Mechanism of Antimetabolite Action

Abstract. The action of an enzyme essential for tryptophan biosynthesis is inhibited by tryptophan and also by an analog of tryptophan. Similarly, histidine and one of its analogs inhibit the action of an enzyme essential for histidine biosynthesis. A mutant resistant to the histidine analog produces an apparently altered enzyme which is insensitive to both the analog and histidine.

Structural analogs of amino acids, purines, and pyrimidines have generally been considered to inhibit growth by interfering competitively with the *incorporation* of the corresponding normal metabolites into essential components of the cell. Evidence has now been obtained that analog action, in certain instances, may be explained by an alternative mechanism in which the analog inhibits the *biosynthesis* of the normal metabolite. Such a mechanism of analog action was suggested by recent observations concerning the control of biosynthetic reactions. Several metabolites, including valine (*1*), isoleucine (*1*), proline (*2*), and cytidine 5′-phosphate (*3*), have each been found to inhibit an enzymatic reaction necessary for its own biosynthesis. This type of inhibition constitutes a negative feedback system which permits the metabolite to regulate its biosynthesis (*1*). It was considered possible that an analog might act by mimicking the specific inhibitory effect of the corresponding metabolite.

This possibility has been confirmed by the finding that DL-6-fluorotryptophan (6-FT) (*4*), as well as tryptophan itself, is a potent inhibitor of the condensation of anthranilic acid with phosphoribosylpyrophosphate, a reaction essential (*5*) for the biosynthesis of tryptophan (Table 1). Similarly, histidine and its analog DL-2-thiazole alanine (2-TA) (*4*) are inhibitors of the synthesis of "compound III," an essential intermediate (*6*) in the biosynthesis of histidine (Table 2). DL-6-Fluorotryptophan is as effective as tryptophan for the inhibition of the condensation of anthranilic acid with phosphoribosylpyrophosphate. On the other hand, 20 times as much 2-TA as histidine is necessary for the inhibition of "compound III" synthesis. The difference in the effectiveness of the two analogs as enzyme inhibitors may be partially reflected in the difference in their bacteriostatic effects on *Escherichia coli* W. Colony diameter is reduced by 50 percent in the presence of $2 \times 10^{-7} M$ 6-FT, whereas 3500 times that amount of 2-TA is required for a similar reduction.

If such an inhibitory effect of an analog on the action of an enzyme necessary for the biosynthesis of the corresponding normal metabolite is indeed responsible for bacteriostasis, then the development of resistance might be accompanied by a decreased sensitivity of the affected enzyme to inhibition by the analog. An alteration of this type has been found in a mutant selected for resistance to $2 \times 10^{-2} M$ 2-TA. The enzymatic synthesis of "compound III" by extracts of this organism is completely insensitive to 2-TA (Table 2) (*7*).

In addition to this change, the enzyme in the mutant has also lost sensitivity to histidine (Table 2), and the organism excretes a compound provisionally identified as histidine. The parent strain, on the other hand, produces precisely enough histidine to meet its needs and does not excrete histidine. These observations provide evidence that the inhibition by histidine of the enzymatic synthesis of "compound III" is responsible for the precision of the feedback control of histidine biosynthesis in the parent strain. Cohen and Adelberg (*8, 9*) have reported excretion of other amino acids by mutants resistant to a variety of analogs, and it seems possible that the loss of feedback control which they postulate involves a mechanism similar to that described here.

The observations that both 6-FT and 2-TA mimic the specific inhibitory effects of their corresponding normal metabolites support a mechanism of analog action involving interference with the control of biosynthetic reactions. If the bacteriostatic effect of 2-TA on the parent strain is the result of such interference, as represented by the inhibition of the enzyme synthesizing the histidine precursor, "compound III," then in the mutant the insensitivity of this enzyme to inhibition by 2-TA accounts for the observed resistance. However, it is also possible that the bacteriostatic action of 2-TA is due to competition with histidine for incorporation into macromolecules. In this case the insensitivity of the enzyme to histidine, leading to the overproduction of this competitive metabolite, could account for the resistance of the mutant to 2-TA. It is hoped that

Table 1. Inhibition of the condensation of anthranilic acid (AA) with phosphoribosylpyrophosphate (PRPP) by tryptophan and by its analog, 6-FT. Phosphoribosylpyrophosphate was generated *in situ* from adenosine triphosphate and ribose-5-phosphate (PRPP kinase is present in excess in these extracts). The rate of condensation was determined according to the method of Yanofsky (*5*); 0.01 ml of an extract of *E. coli* W (12 mg of protein per milliliter) was used.

Inhibitor and concn. (M)	Inhibition of AA, PRPP condensation (%)
None	0*
L-tryptophan (5×10^{-5})	45
L-tryptophan (5×10^{-4})	62
6-FT (5×10^{-5})	40
6-FT (5×10^{-4})	80

* In the absence of an inhibitor 10.0 mμmole of anthranilic acid was metabolized in 10 minutes.

Table 2. Inhibition of "compound III" synthesis. The rate of synthesis was determined by a previously described method (*6*); 0.2 ml of extract (12 mg of protein per milliliter) was used. Extracts were prepared by sonic oscillation from a mutant resistant to DL-2-thiazole alanine (2-TA) and from the wild type, *E. coli* W.

Inhibitor and concn. (M)	Inhibition of "compound III" synthesis (%)	
	Wild type extract	Resistant mutant extract
None	0*	0*
L-Histidine (1×10^{-4})	59	< 1
L-Histidine (2×10^{-4})	73	< 1
L-Histidine (3×10^{-2})		< 1
2-TA (8×10^{-4})	28	< 1
2-TA (2×10^{-3})	57	< 1

* In the absence of an inhibitor 74 and 39 mμmole of "compound III" were synthesized in 15 minutes by extracts of the sensitive and resistant strains respectively.

studies of the kinetics of histidine biosynthesis by the mutant and by the parent strain will permit us to determine which of these mechanisms is responsible for the bacteriostatic effect of 2-TA (*10*).

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7 November 1958

Isolation of Gelatin from Ancient Bones

Abstract. The isolation and characterization of gelatin from 12,000-year-old deer antlers is described. Use of gelatin from ancient bones for carbon-14 dating may improve the accuracy of the dating procedure because gelatin is not likely to be contaminated by extraneous carbon.

Estimates of the age of buried objects based on their carbon-14 content has been of great value in anthropology. We believe that gelatin from ancient bones might be used for such dating with advantage. Charcoal has been the material most extensively used by anthropologists for dating. It is assumed that carbon produced by pyrolysis of ancient materials could not subsequently be contaminated with contemporary carbon. Charcoal, however, is not always pure carbon (*1*) but is, rather, a complex organic material. It presents a large surface area and may absorb other organic substances.

It is necessary to separate the organic and inorganic carbon fractions of bone before the count is made, because calcium carbonate in the mineral matrix may exchange with contemporary carbon dioxide of the air or ground water (*2*). Furthermore, ancient bones are porous and are capable of absorbing organic material from the soil.

Approximately 80 percent of the carbon of bone is collagen carbon, constituting 8.7 percent of air-dried bone. Collagen is soluble in hot water, in which it dissociates into a soluble protein gelatin. With time, the amount of this collagen decreases. However, appreciable amounts of collagen may be found in bone up to 100,000 years old (*3*). Gelatin is 18 percent nitrogen. The alpha-amino nitrogen of gelatin is 14 percent. In humic acids the alpha-amino nitrogen is between 0.2 and 1.5 percent (*4, 5*). The hydroxyproline content of gelatin is 13.5 percent; of humic acids, less than 0.05 percent.

We have attempted to prepare gelatin from approximately 10 g of deer antler (*6*). The deer antler was the remainder of radiocarbon sample Y-158, approximately 12,000 years old (*5*). Ten grams of pulverized antler were extracted with three 50-ml portions of 10 percent Versene, *p*H 7.05, in a boiling water bath for 1-hour periods with occasional shaking. The pooled extractions were dialyzed on a rocking dialyzer against distilled water at 2°C for 72 hours with eight water changes. After the dialysate had been concentrated in a vacuum to 50 ml, the solution was made 5 percent in trichloroacetic acid and allowed to stand overnight at 2°C. The precipitate was removed by centrifugation, and the supernatant was dialyzed as before. The gelatinous precipitate which formed was filtered and dried. It weighed 249 mg.

The material collected was dissolved in H_2O at room temperature with the addition of a small amount of NaOH which brought the *p*H of the solution to between 4.0 and 4.5. A 1-percent solution of this material gelled at 2°C.

The molecular weight of this gelatin was estimated by the viscosity procedure of Pouradier and Venet (*7*). A molecular weight of 41,000 was obtained. Such a molecular weight is not significantly different from that of commercial gelatins isolated from fresh bone.

Hydroxyproline determinations (*8*) on material dried in a vacuum oven at 100°C for 24 hours indicated that this material contained 12.9 percent hydroxyproline (the usual literature value is 13.5 percent) and 17.4 percent nitrogen (the usual literature value is 13 percent). The carbon content was 96.0 percent of theoretical. The material did not contain detectable amounts of tyrosine (*9*) or uronic acid (*10*).

This material was apparently gelatin of a purity of at least 96 percent. We feel that carbon-14 dating of purified gelatin would be as reliable as charcoal dating, or possibly more so, since analytical evidence may be obtained that the organic material is what it appears to be, namely bone protein (*11*).

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14 November 1958

Proposed System of Terminology for Preparations of Adrenocorticotropic Hormone

Abstract. During the past few years there has been a considerable amount of confusion with respect to the terminology used for adrenocorticotropins (ACTH) isolated from the pituitary glands of various species. In this paper (*1*) a unified system of nomenclature for these hormones is proposed. It is hoped that this system will furnish readily and at a glance, from the terminology itself, pertinent information about the source of the particular preparation as well as the chemical formula of any active degraded product derived from the natural hormone.

Some confusion among investigators is usually unavoidable with respect to the term or name used to designate a biologically active substance derived from natural products before it is isolated in pure form and before its structure is known. The confusion is compounded when preparations of the same substance isolated from tissues of different species differ chemically but have similar biological effects. The terminological problem becomes even more complicated when the pure substances can be modified chemically without loss of biological activity. The present state of the terminology used to designate the adrenal-stimulating substance from the adenohypophysis is a case in point.

Since the discovery of the existence of adrenal-stimulating activity in pituitary glands by Smith in 1927 (*2*), many names have been proposed for the hormone: adrenotropic hormone, adrenocorticotropic hormone, corticotropic hormone, adrenotropin, corticotropin, adrenocorticotropin, and ACTH. In the past few years, adrenal-stimulating pep-

Table 1. Structural differences among adrenocorticotropins isolated from pig, sheep, and beef pituitary glands.

Structure of bovine ACTH:

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Try-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

NH_2
|

Lys-Val-Tyr-Pro-Asp-Gly-Glu-Ala-Glu-Asp-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39

Species	Laboratory	Amino acid residue in position 25 26 27 28 29 30 31 32 33
Pig	Armour Company (*12*)	Gly-Ala-Glu-Asp-Asp-Glu-Leu-Ala-Glu NH_2 |
Pig	American Cyanamid Company (*7*)	Asp-Gly-Ala-Glu-Asp-Glu-Leu-Ala-Glu NH_2 |
Sheep	University of California (*10*)	Ala-Gly-Glu-Asp-Asp-Glu-Ala-Ser-Glu NH_2 |
Beef	University of California (*13*)	Asp-Gly-Glu-Ala-Glu-Asp-Ser-Ala-Glu

tides have been prepared in highly purified form from sheep (*3, 4*), pig (*5–8*), and beef (*9*) pituitaries, and their amino acid sequences (*10–13*) are known. Three different names have been employed by the investigators to designate their products: corticotropin A (*5, 8*) and β-corticotropin (*6*) for the porcine hormone, and α-corticotropin (*3*) for the ovine hormone. In addition, Brink *et al.* (*14*) named an ACTH-active product obtained from peptic digests of porcine ACTH concentrates corticotropin-B. It is the purpose of this note to propose a system of terminology for the adrenal-stimulating hormone and its degraded products possessing biological activity. As far as I am aware, no discussion of this sort has appeared in print, and I hope that these remarks will serve to stimulate further discussion among investigators who are actively interested in the field of pituitary hormones.

At the outset, the hormone, regardless of the species, should be called *adrenocorticotropic hormone* (ACTH) or *adrenocorticotropin*. The terms "adrenotropic hormone" and "adrenotropin" should not be employed, for they imply that the hormone stimulates the whole adrenal gland. It is established now beyond any doubt that the hormone controls only the development and function of the cortical part of the adrenal gland. Similarly, the designation of the hormone as "corticotropic hormone" or "corticotropin" may lead to confusion, for many other glands, such as the cerebrum, kidney, lymph gland, thymus, and ovary, all have cortices.

Although adrenocorticotropins isolated from unhydrolyzed extracts of pig, sheep, and beef pituitaries possess biological properties similar to one another, there are slight differences among them in amino acid composition as well as structural sequence. Adrenocorticotropins from these three species are single-chain polypeptides composed of 39 amino acids with serine and phenylalanine as N- and C-terminal residues, respectively (*9, 15*). The only difference in amino acid composition between the porcine and ovine hormones appears to be one more leucine in the former and one more serine in the latter; this difference occurs in the sequence

. . . Ala-Ser . . .
31 32

which appears in the ovine peptide in place of the

. . . Leu-Ala . . .
31 32

sequence in the porcine peptide. Although there are no differences in amino acid composition between the ovine and bovine hormones, their sequential isomerism seems to support the conclusion that the ovine and bovine adrenocorticotropins are distinct chemical entities. Table 1 summarizes the structural differences that exist among these adrenocorticotropins. Because of the differences, it is necessary to distinguish among adrenocorticotropins isolated from glands of the various species, and a suggestion might be made that the polypeptides possessing ACTH activity obtained from unhydrolyzed extracts of sheep, pig, and beef pituitaries be designated α_s-, α_p- and α_b-adrenocorticotropin, respectively. If more than one active component can be derived from the unhydrolyzed extract, as in the case of the sheep (*3, 4*) and pig (*6*) hormones, these could be called β_s-, γ_s-, or β_p-, γ_p-, and so on down the alphabet.

It is now well established that removal of certain portions from the C-terminus of the hormone does not cause loss of activity (*15*). Such active fragments that have been obtained by *enzymic* action could be distinguished by the species letter in subscript and the remaining amino acid sequence in superscript; for example, α_s^{1-28}-ACTH would represent the active fragment obtained by the action of pepsin, which cleaves 11 amino acids from the C-terminus of the ovine α_s-ACTH (*15, 16*). There is some evidence (*15*) that as many as 15 amino acids can be removed from this terminus without damage to the activity. Since the amino acid sequence of the first 24 residues from the N-terminus is identical for the three species (Table 1), then in this case, particularly if the synthetic peptide with this amino acid sequence, namely,

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-
1 2 3 4 5 6 7 8

Try-Gly-Lys-Pro-Val-Gly-Lys-Lys-
9 10 11 12 13 14 15 16

Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro
17 18 19 20 21 22 23 24

is biologically active, the subscripts s, p, and b could be omitted and the active peptide could be designated as α^{1-24}-adrenocorticotropin or α^{1-24}-ACTH.

CHOH HAO LI

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3 October 1958

Effect of Synthetic Lysine Vasopressin on Adrenocortical Secretion

Abstract. By means of direct arterial perfusion of the adrenal glands in the dog it has been shown that synthetic lysine vasopressin stimulates the secretion of hydrocortisone. This effect is not mediated via the adenohypophysis or any other organ but is rather the result of direct stimulation of the adrenal cortex by vasopressin itself.

The relation between the secretion of vasopressin and its effect on adrenocortical activity has not been satisfactorily elucidated. Several workers (*1*) have published data supporting the hypothesis of direct ACTH release induced by vasopressin, whereas other evidence has accumulated which would tend to invalidate this concept (*2*).

In view of certain reciprocal relationships between vasopressin and adrenocortical hormones (*3*), and because the locus or mode of action of vasopressin is not clear, it occurred to us that vasopressin might directly stimulate the adrenal cortex. The adrenal perfusion technique was felt to be an ideal method for studying this problem (*4*).

Dogs, anesthetized with sodium pentobarbital (0.5 mg/kg), were hypophysectomized (*5*), and the adrenals were then prepared for perfusion by the technique of Hilton *et al.* (*6*).

Donor hypophysectomized dogs were bled from a femoral artery the morning of the experiment, and this arterial blood was then perfused by a mechanical pump into the adrenal preparation of the recipient hypophysectomized animal. The recipient animal's heart was then fibrillated to insure noncontamination of the donor blood.

Synthetic lysine vasopressin (*7*) was added to the arterial circuit leading to the adrenal glands at the rate of 1 ml/min for 7 to 10 minutes. The concentrations used varied from 0.2 to 0.3 pressor unit per milliliter (0.7 to 1.0 μg). The blood-flow rate through the glands was kept constant at 10 ml/min throughout each experiment. At the end of each experiment an injection of ACTH at a rate of 1 ml/min for 7 to 10 minutes and at a concentration of 0.5 to 2.5 units per milliliter was given to verify adrenal viability.

The adrenal venous blood was collected in graduated cylinders, the rate of flow was measured, and the concentration of hydrocortisone in the plasma was determined by the method of Peterson *et al.* (*8*). None of the adrenal venous effluent was allowed to return to the recipient animal.

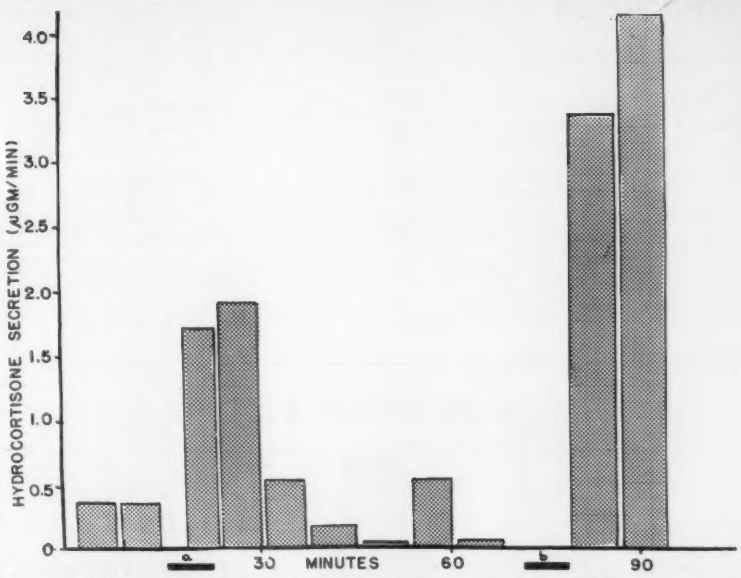

Fig. 1. Following two control periods, at *a*, lysine vasopressin was administered at the rate of 0.3 unit per minute for 7 minutes. At *b*, ACTH was administered at the rate of 1.0 unit per minute for 7 minutes.

Six experiments were performed, and a representative example is shown in Fig. 1. In this experiment, it may be seen, there was a sixfold increase (*9*) in hydrocortisone secretion from the perfused adrenal glands after the administration of vasopressin. The effect was largely dissipated 15 minutes after the end of the injection period. In general, this was the pattern in the six experiments.

It may also be noted from Fig. 1, that following ACTH administration there was a large increment in hydrocortisone secretion. The response to ACTH was greater than that to vasopressin and also indicated satisfactory viability of the preparation. This type of response to ACTH was noted in four of the six experiments; in two experiments the response to vasopressin was greater than that to ACTH.

A mild pressor response within the adrenal arterial circuit was noted in all six experiments, incident to vasopressin administration; the mean rise in blood pressure varied from 10 to 65 mm-Hg, with an average rise of 16 mm.

Our experiments, in which we used the direct perfusion technique, which eliminates any interference from other endocrine glands or organs, indicate that synthetic lysine vasopressin has a direct stimulatory effect on the adrenal glands. These findings raise the question as to whether vasopressin may be an important factor in the "stress" mechanism.

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16 January 1959

Meetings

Seaweed Symposium

The third international seaweed symposium was held in Galway, Eire, on 13 to 19 Aug. 1958. It differed from its predecessors in that four formal lectures were delivered by invited speakers and in that an exhibition of commercial seaweed products was organized. Previous symposia were held in Edinburgh (in 1952) and in Trondheim (in 1955).

The participants, who came from 22 countries, numbered 207. The symposium was opened officially by Sean Lemass, Minister for Industry and Commerce. All scientific sessions were held at University College, Galway. In addition there were excursions into the surrounding country, either to collect algae or to visit the seaweed factories at Kilkeerin and Ballyconneely.

The symposium was organized under the auspices of a small international advisory committee through the Irish National Committee, but most of the work was done by a local committee in Galway with T. Dillon as chairman and C. O'hEocha as secretary. The program was divided into three sections: botany, chemistry, and applied industry, with a special session on intertidal ecology. Special lectures were given by R. D. Preston (England), on "Biochemical and biophysical aspects of some seaweeds"; by E. L. Hirst (Scotland), on "Seaweed mucilages"; and by H. M. Ulrich (Austria), on "Alginate esters and altered alginate fibers." A. Walford (United States) delivered a public lecture on "The sea as a potential source of food."

Some 20 communications of original work were made to the chemistry section. Wickberg (Sweden) reported the isolation of O-α-D-galactopyranosyl-glyceritol, O-α-D-galactopyranosyl-(1-6)-O-β-D-galactopyranosyl(1-1)-D-glyceritol, mytilitol, and 2-L-amino-3-hydroxy-1-propanesulfonic acid and an N-substituted taurine from various red seaweeds. The presence of unidentified phenolic compounds in *Ascophyllum nodosum* has been detected by Haug and Larsen (Norway). These workers also determined that the seasonal variation of nicotinamide in some of the Fucaceae is between 15 and 35 micrograms per gram of dry matter, in autumn and spring, respectively. Turvey and Rees (Wales) described the major water-soluble polysaccharides of *Porphyra* as floridean starch and a galactan sulfate, containing galactose, methyl galactose, and anhydrogalactose. O'Donnell and Percival (Scotland) reviewed the polysaccharides in green seaweeds and described especially a heteroglycan sulfate from *Spongamorpha* which contained glucose, xylose, rhamnose, and glucuronic acid. The hydrolysis of the sulfate ester linkage in fucoidin, chondroitin sulfate, and keratosulfate by an esterase in *Patella vulgata* was reported by Lloyd and Lloyd (Wales). A preliminary description of the polysaccharide sulfate from *Furcellaria* was given by Clancy, Walsh, O'Colla and Dillon (Eire). Young and Smith (Nova Scotia) reported analyses of the free amino acids, peptides, and proteins of *Chondrus* in which some peptides contained citrulline and ornithine and in which about 50 percent of the protein was present in an insoluble form, the distribution of amino acids being very similar to that of other algal proteins.

About ten papers on the utilization of marine algae were read. A critical appraisal of laminarin sulfate as a blood anticoagulant was given by Burt (Scotland); she stressed the fact that this ester is of lower potency and of much greater toxicity than heparin, on prolonged administration to rabbits and dogs. Seaweed meal can be fed to chickens, hens, and sheep without detrimental effects, according to Jensen (Norway), and with beneficial effects when it constitutes 5 to 7 percent of the basal ration, according to Höie and Sannan (Norway).

About 27 papers were read in the botany section. From experimental work Jacobs (United States) reported that the controlling factors in wall formation and regeneration in *Caulerpa prolifera* must be in the cytoplasm close to the cell wall, rather than in the streaming cytoplasm. Segi (Japan) discussed the commercial cultivation of *Monostroma* in Japan.

Boalch (England) described changes in the proportions of prostrate and erect systems in pure cultures of *Ectocarpus confervoides*, and changes in shape and size of cell, which resulted from changes in salinity, illumination, and temperature. The study throws some doubt on the reliability of current taxonomic criteria. Dixon (England) discussed confusion in the taxonomy of *Pterocladia pinnata* caused by morphological variation as a result of differing ecological factors. Müller-Stoll (Germany) reported on the ecology, internal anatomy, and biochemistry of *Fucus vesiculosus* in the western Baltic. In deeper waters this species grows to a length of 7 meters and lives 7 years or more. Powell (Scotland) discussed his proposal to reduce the 15 or more species of *Fucus* now listed to about five.

Baardseth (Norway) described a method of physode estimation and reported that the percentage of physode volume varied with the species and, in *Ascophyllum*, was related to salinity.

Haxo and Neushal (United States) have studied the growth and differentiation of young specimens of *Macrocystis pyrifera* and described an ingenious apparatus for growing and observing these plants at depths of 30 to 100 feet. This technique permits analysis of the effects of various environmental factors. Fogg (England) reviewed the technology of mass culture of microscopic marine algae but concluded that harvesting difficulties make such culture commercially uneconomic at present. Von Stosch (Germany) compared the leucosin of diatoms and chrysomonads with laminarin and adduced evidence for their close relationship.

Kanwisher (United States) described a new method of determining the photosynthetic and respiratory capacity of several intertidal algae. He reported that freezing and drying on the shore have similar effects in depressing respiration. Provasoli (United States) has observed the response of *Ulva lactuca* to various hormones added to bacteria-free cultures. His study suggests strongly that the level of auxin and gibberellin controls speed of growth and size of crop in the coastal zone.

Allen (United States) has induced several fresh-water, nitrogen-fixing species of blue-green algae to become adapted to marine conditions. Growth was somewhat retarded, but their ca-

pacity to fix nitrogen under these conditions was studied.

Grenager (Norway) described a method of predicting the distribution of *Laminaria digitata* and *Ascophyllum nodosum* in unknown areas by study of charts only. A forecast was checked later by a field survey and found to deviate by only a few percent for each species.

The abstracts of most communications and of two of the formal lectures have been printed in a small volume of 92 pages, which may be purchased from Dr. C. O'hEocha, University College, Galway, Eire. No further printing of the proceedings is anticipated. The next symposium will be held in Paris in 1961, under the chairmanship of A. D. de Virville.

CONSTANCE I. MACFARLANE
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Youth Conference on the Atom

A national Youth Conference on the Atom, the first meeting of high-school science students and teachers for discussion of the peaceful uses of nuclear energy, will be held at the Claridge Hotel in Atlantic City, N.J., 30 April–1 May. The attendance of approximately 500 junior and senior high-school science students and teachers at the conference will be sponsored by 60 or more electric utility companies throughout the country. Organizations cooperating in the conference include the AAAS, Atomic Industrial Forum, Future Scientists of America Foundation, National Science Foundation, National Science Teachers Association, and Science Clubs of America.

John A. McCone, chairman of the Atomic Energy Commission, will deliver an address on 30 April. Other speakers will be Norman C. Hilberry, director of the Argonne National Laboratory; Charles E. Robbins, executive manager of the Atomic Industrial Forum, who will tell the young scientists about industrial uses of the atom; Cyril Comar, director of the Laboratory of Radiation Biology at Cornell University, who will describe the use of the atom in agriculture; and John Laughlin, chief of the division of physics at the Sloan-Kettering Institute for Cancer Research, who will speak on the uses of the atom in medicine.

Forecasts of the atom and the world of tomorrow will be presented by Francis K. McCune, vice president of the General Electric Company, and Charles H. Weaver, vice president of the Westinghouse Electric Corporation, who are in charge of atomic activities at their respective companies. Ben D. Wood, director of the Bureau of Collegiate Educa-

tional Research at Columbia University, is serving as educational consultant to the conference.

The program for the Youth Conference is being arranged by the Electric Companies Public Information Program. For information, write to Bozell and Jacobs, Inc., 2 W. 45 St., New York 36, N.Y.

Operational Research

The second International Conference on Operational Research, organized by the International Federation of Operational Research Societies, will be held in Aix-en-Provence, France, 5–10 September 1960. The program committee would welcome suggestions for papers (or groups of papers) to be presented at the conference. Suggestions should be sent to the Secretary of IFORS, 11 Park Lane, London W.1, England, *before 1 May 1959*, with a copy to the secretary of the Operational Research Society of the country of origin. Manuscripts will be required by *1 December 1959* in order that preprints can be made available before the conference.

The International Federation came into existence in January this year, having as its objects "the development of operational research as a unified science and its advancement in all nations of the world." The first international conference on the subject was held at Oxford in 1957.

Prague Antibiotics Conference

A symposium on antibiotics with international participation will take place in Prague, Czechoslovakia, 17–23 May. The proceedings will be divided into three sections: (i) problems of the biosynthesis of antibiotics, (ii) the scientific pathophysiological basis of antibiotic therapy, and (iii) the problems of fermentation technology and nonmedical use of antibiotics.

Further information will be furnished upon request by the secretary of the symposium, Dr. M. Heřmanský, Antibiotics Research Institute, Roztoky near Prague Czechoslovakia.

Forthcoming Events

May

10–15. Society of American Bacteriologists, St. Louis, Mo. (E. M. Foster, Univ. of Wisconsin, Madison 6.)

10–14. American Soc. of Maxillofacial Surgeons, Chicago, Ill. (O. H. Stuteville, 700 N. Michigan, Chicago 11.)

11–12. Practical Problems of Coordinating and Integrating All Services Related to the Treatment, Training and Management of the Mentally Retarded,

conf., Vineland, N.J. (J. D. Eadline, Training School, Vineland, N.J.)

11–13. Instrumentation and Computation in Process Development and Plant Design, symp., London, England. (Institute of Chemical Engineers, 16, Belgrave Sq., London, S.W.1.)

11–13. Microwave Theory and Techniques, natl. symp., Boston, Mass. (H. Pratt, Inst. of Radio Engineers, 1 E. 79 St., New York 21.)

11–13. Power Instrumentation, natl. symp., Kansas City, Mo. (H. H. Johnson, Consolidated Edison Co. of New York, Room 1515-S, 4 Irving Pl., New York 3.)

13. New Orleans Acad. of Sciences, annual, New Orleans, La. (J. J. Creely, U.S. Dept. of Agriculture, 1100 Robert E. Lee Blvd., New Orleans, La.)

13–16. Human Biochemical Genetics, Ciba Foundation symp., London England. (G. E. W. Wolstenholme, Ciba Foundation, 41 Portland Pl., London, W.1.)

14–15. Operations Research Soc. of America, Washington, D.C. (H. J. Miser, Rt. 2, Box 211, Vienna, Va.)

14–16. Acoustical Soc. of America, Ottawa, Canada. (W. Waterfall, 335 E. 45 St., New York 17.)

14–17. American Acad. of Dental Medicine, 13th annual, Atlantic City, N.J. (H. A. Lentz, 619 Main Ave., Passaic, N.J.)

14–16. American Assoc. of Physical Anthropologists, Madison, Wis. (E. E. Hunt, Jr., Peabody Museum, Harvard Univ., Cambridge 38, Mass.)

17–20. American Inst. of Chemical Engineers, 40th natl., Kansas City, Mo. (F. J. Van Antwerpen, AICE, 25 W. 45 St., New York 36.)

17–21. American Ceramic Soc., 61st annual, Chicago, Ill. (C. S. Pearce, ACS, 4055 N. High St., Columbus 14, Ohio.)

17–21. Institute of Food Technologists, 19th annual, Philadelphia, Pa. (C. S. Lawrence, IFT, 176 W. Adams St., Chicago 3, Ill.)

17–23. Antibiotics, intern. symp., Prague, Czechoslovakia. (M. Heřmanský, Antibiotics Research Inst., Roztoky near Prague, Czechoslovakia.)

17–23. Mass Spectrometry, 7th, Los Angeles, Calif. (A. G. Sharkey, Jr., U.S. Bureau of Mines, 4800 Forbes Ave., Pittsburgh 13, Pa.)

18–20. Instrumental Methods of Analysis, 5th natl. symp., Houston, Tex. (H. S. Kindler, Director of Technical and Educational Services, ISA, 313 Sixth Ave., Pittsburgh 22, Pa.)

19–23. American Assoc. of Mental Deficiency, Milwaukee, Wis. (N. A. Dayton, Mansfield State Training School & Hospital, Mansfield Depot, Conn.)

20–22. Education of the Scientist in a Free Society, conf., Milwaukee, Wis. (A. B. Drought, College of Engineering, Marquette Univ., 1515 W. Wisconsin Ave., Milwaukee 3.)

21–23. American Assoc. for the History of Medicine, 32nd annual, Cleveland, Ohio. (Miss E. H. Thomson, Yale Univ. School of Medicine, New Haven, Conn.)

21–27. Veterinary Cong., 16th intern., Madrid, Spain. (J. Jensen, General Secretary of Permanent Committee, Belstraat 168, Utrecht, Netherlands; or W. A. Hagan, Dean, Cornell Univ., New York State Veterinary College, Ithaca, N.Y.)

24–27. Chemical Inst. of Canada, 42nd annual conf., Halifax, Nova Scotia. (Chemical Inst. of Canada, 18 Rideau St., Ottawa 2, Ontario.)

24–29. American Tuberculosis Assoc., Chicago, Ill. (Mrs. W. B. White, 1790 Broadway, New York 19.)

24–29. Social Welfare, natl. conf. and annual forum, San Francisco, Calif. (National Conference on Social Welfare, 22 W. Gay St., Columbus 15, Ohio.)

25–27. American Gynecological Soc., Hot Springs, Va. (A. A. Marchetti, 3800 Reservoir Rd., NW, Washington 7.)

25–27. American Soc. for Quality Control, Cleveland, Ohio. (L. S. Eichelberger, A. O. Smith Corp., Milwaukee, Wis.)

25–27. Chemical Inst. of Canada, 42nd annual conf., Halifax, Nova Scotia. (Chemical Inst. of Canada, 18 Rideau St., Ottawa, Ontario, Canada.)

25–27. Telemetering, natl. conf., Denver, Colo. (R. Schmidt, AVCO Mfg. Co., 201 Lowell St., Wilmington, Mass.)

25–28. Smoking and Lung Cancer, and Pulmonary Emphysema, symps., American Trudeau Soc., Chicago, Ill. (H. W. Harris, Medical Sessions Committee, ATS, 1790 Broadway, New York 19.)

26–29. American College of Cardiology, Philadelphia, Pa. (P. Reichert, 480 Park Ave., New York 22.)

(*See issue of 20 March for comprehensive list*)

Equipment

The information reported here is obtained from manufacturers and from other sources considered to be reliable, and it reflects the claims of the manufacturer or other source. Neither Science *nor the writer assumes responsibility for the accuracy of the information. A coupon for use in making inquiries concerning the items listed appears on page 982.*

■ DIFFERENTIAL TRANSFORMER with large diameter is designed for applications in which the core must be separated from the coil by a glass or other nonmagnetic tube. The transformer has a linear range of 1 in. in either direction from null position. Deviation from linearity is less than 1 percent over the full range. (Schaevitz Engineering, Dept. 725)

■ DIGITAL SUBTRACTOR-CONVERTER accepts two digital input signals, subtracts one from the other digitally, and presents an analog output signal proportional to the difference. Input signals are accepted at pulse rates up to 250 kcy/sec in blocks occurring at 1/30 sec intervals. Each block may contain up to 4095 pulses. Output voltage is ±50 mv for a ±1 count difference and up to ±10 v for a ±200 count difference. Output accuracy is ±2 percent or 10 mv, whichever is greater. (Computer Equipment Corp., Dept. 727)

■ POTENTIOMETER CHECKER consists of a ten-turn master potentiometer mechanism for coupling the potentiometer under test, a recorder, drive mechanisms and trimming adjustments for zeroing and error, and a calibration source. The master-potentiometer output voltage is a linear function of test-potentiometer shaft rotation with accuracy ranging from 0.01 percent for the one-turn output shaft to 0.003 percent for the 15-turn output shaft. (Analog Controls, Inc., Dept. 734)

■ AMPLIFIERS for oscillograph recorders drift less than 0.5 mv equivalent input per hour and will operate from 115v ±5v power lines without additional regulation. Input impedance is 2 megohm. Frequency compensation for galvanometer characteristics is designed for plug in. Automatic signal overload protection prevents galvanometer burnout. (Epsco, Inc., Dept. 723)

■ VACUUM PUMPING SYSTEM is a 3-in. system with a separate roughing line for initial evacuation of the bell jar. Pumping time to 10^{-5} mm-Hg is 20 min. Ultimate pressure is 5×10^{-6} mm-Hg. Ionization and thermocouple gages measure vacuum. (Bon-De Electronic Laboratories, Inc., Dept. 731)

■ DIGITAL RECORDER is a self-balancing, null-type indicator recorder for full scale of 0 to 100 mv. Minimum printing cycle is 3 sec, and full-scale response time is 3 sec. Accuracy is ±0.5 percent. (Research Appliance Co., Dept. 729)

■ POWER-DENSITY METER measures power density of high-level microwave fields. The meter reads directly from 1 to 20 mw/cm² with accuracy of −0, +2 db. Three standard types cover the frequency ranges 2700 to 3300, 5200 to 5900, and 8500 to 9600 Mcy/sec. The meters are battery-operated and self-calibrating. Total weight is 6 lb, including batteries. (Sperry Microwave Electronics Co., Dept. 732)

■ PHASE METER for the frequency range from 15 to 500 Mcy/sec consists of a phase-indicator unit and a time-delay unit. The former indicates when input signals are in phase or 180 deg out of phase. Minimum input signal is 1 v r.m.s. with panel meter or 20 μv with external receiver detector. Accuracy is ±0.05 deg or ±1 percent up to 200 Mcy/sec and ±2 percent at 500 Mcy/sec. (AD-YU Electronics Laboratory, Inc., Dept. 733)

JOSHUA STERN

National Bureau of Standards, Washington, D.C.

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Applications, accompanied by a recent photograph or snapshot and giving age, nationality, and other personal information; list of publications, and names and addresses of three references, should be submitted to the Head, Department of Plant Science, University of Alberta, 1 June 1959. 4/10

Botanist-Bacteriologist. Ph.D. or equivalent, to teach bacteriology and some botany. Rank of assistant professor. Write Professor W. B. Stallworthy, Department of Biology, Mount Allison University, Sackville, New Brunswick, Canada. ew tf

(a) Chief, Division of Chemistry, 450-bed teaching hospital; Ph.D. required; $8000–$10,000; large city. Midwest; important medical center. **(b) Research Director;** staff of 20 graduate level researchers in field of veterinary pharmaceuticals and biologicals; $13,000–$18,000; Midwest. **(c) Ph.D. and Ph.D.-M.D. Pharmacologists;** duties consist of making investigations in clinical research with ranks of associates; advantageous if qualified physiology or biochemistry also; $10,000–$15,000; residential town near New York City. **(d) Young Ph.D. Biochemist;** group association; capable administrator required; $8000–$10,000; California. **(e) Virologist,** M.S. or Ph.D.; experienced in tissue culture and serology and, also, microbiologist, Ph.D.; research laboratories; large city in East, four medical schools. S4-1 Medical Bureau, Burneice Larson, Director, 900 North Michigan Avenue, Chicago. X

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(*Continued on page 982*)

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10 April 1959

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Space vehicle development, including basic planning, development, contract coordination, and operational programming and planning for manned and unmanned satellites. Systems studies for auxiliary power supplies, air regenerative systems, instruments, guidance and communication equipment for space vehicles.

Space probes: Development and operation of vehicles, payload and instrumentation, programming and operation of flight, trajectory, communication systems, and ground support systems for near space and deep space probes.

Beltsville

SPACE MECHANICS

Experimental and analytical study of orbital mechanics including parameters of preliminary and refined orbits, ephemerides, lifetimes, equator crossings and perturbations.

Beltsville; Langley; Ames

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Developmental studies of boosters, launchers, multi-stage engines, guidance and attitude control systems for space vehicles.

Basic research on the interrelationships between electrical, magnetic and thermodynamic energy, and application of such knowledge to space propulsion.

Magneto hydrodynamics: Research on plasma and ion accelerators for space propulsion and auxiliary power systems.

Research on reactors and reactor shielding for aeronautical and space propulsion systems.

Beltsville; Lewis

AERODYNAMICS AND FLUID MECHANICS

Investigation of the thermodynamics and transport properties of gases at high temperatures as encountered in entry into planetary atmosphere.

Research on performance, stability and control, automatic guidance, and navigation for subsonic, supersonic, and hypersonic aircraft.

Aerodynamic heating and satellite re-entry phenomena.

Langley; Ames; Lewis; High-Speed Flight Station

(Positions are filled in accordance with Aeronautical Research Announcement 61B)

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Research and development of new sensing devices and instrumentation techniques in electronics, optics, aerodynamics, mechanics, chemistry and atomic physics.

Systems studies and evaluation of control, guidance, navigation, and communication equipment for space vehicles and other high performance applications requiring rugged and compact design.

All Facilities

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Experimental programs and evaluation studies of astronomical and geophysical measurement and scientific equipment used in space vehicle payloads.

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Beltsville

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Investigation of the characteristics of high temperature structures and materials. Study of fatigue, structural stability, and other problems of structural dynamics.

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RESEARCH FACILITY ENGINEERING

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Langley; Ames; Lewis

Please address your inquiry concerning any of the programs listed here to the Personnel Director of the appropriate NASA research center:

Langley Research Center, Hampton, Virginia
Ames Research Center, Mountain View, California
Lewis Research Center, Cleveland, Ohio
High-Speed Flight Station, Edwards, California
Beltsville Space Center, 4555 Overlook Ave., Washington, D. C.

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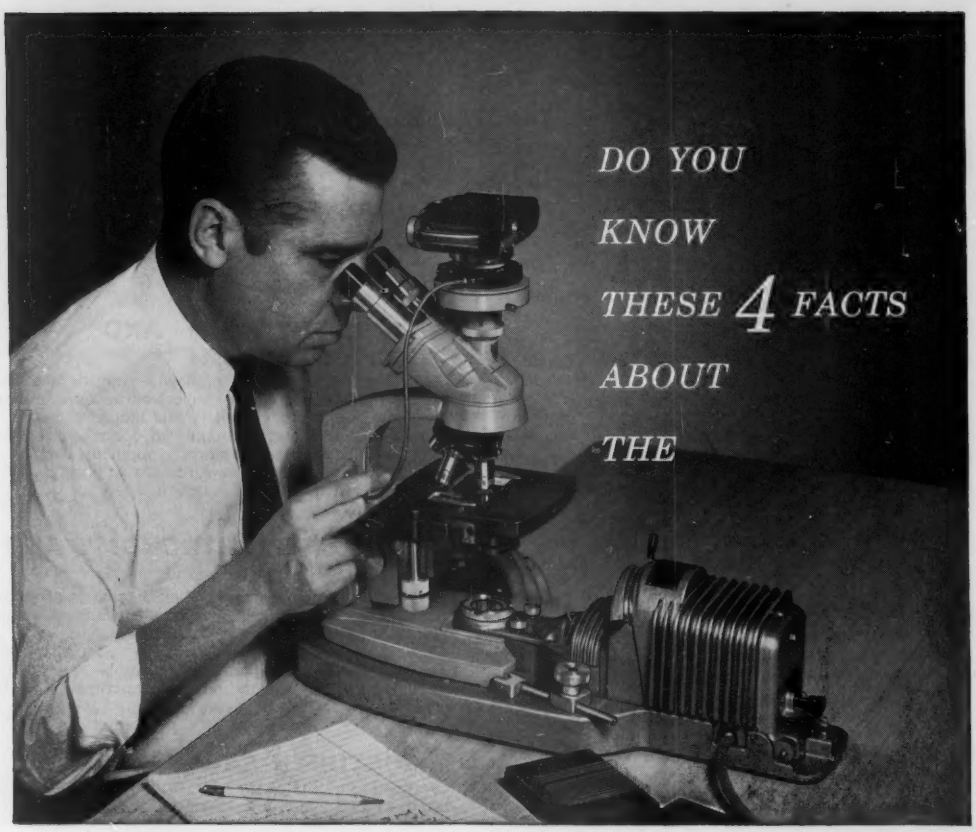

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